Principles and Practice
of Travel Medicine

Principles and Practice **of Travel Medicine**

SECOND EDITION

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Preface

Travel medicine: where have we been, where are we now and where are we going are the intriguing and pertinent issues to consider. Where have we been? We have come a long way since the age of Galileo: 'Yet I do seriously and on good grounds affirm it possible to make a flying chariot in which a man may sit and give such a motion unto it as shall convey him through the air' (John Wilkins, 1640), through to the Wright brothers inventing and building the first successful aeroplane in 1903. Where are we now? With the Airbus A380, the largest passenger airliner in the world, taking travellers with increasing speed to numerous destinations around the globe. And where are we going? With 430 travellers signed up to fly with Virgin Galactic, travel to space may yet prove to be the ultimate tourist destination. We really have travelled a long, long way . . . and we will continue to do so. The ever-increasing need for travel medicine specialists to meet the travel health needs of travellers could not be more evident.

This second edition of the *Principles and Practice of Travel Medicine* aims to provide practitioners with a reference resource to support the clinical practice of travel medicine. Several chapters have been updated: the new chapter dedicated to malaria includes recommendations for prophylaxis and strategies for stand-by self-treatment, while the chapter on vaccine-preventable diseases includes new developments in licensed vaccines as well as continent-based recommendations for their administration. Other important topics of clinical practice include the travel health management of high-risk travellers, who should always be evaluated with care and advised accordingly. They include the diabetic traveller, the immunocompromised, those with cardiovascular, renal, neurological, gastrointestinal, malignant and other disorders, psychological and psychiatric illnesses, pregnant women, children and the elderly. New chapters address other emerging clinical travel medicine issues such as health tourism and considerations on meeting the travel health needs of those visiting friends and relatives, alongside the updated chapter on the important topic of migrant health. With increasing numbers of more adventurous travellers tackling travel at altitude for example, the chapter on travel medicine and extreme environments will be of particular interest to those whose practice involves meeting the travel health needs of such intrepid travellers. Of course the most intrepid will be those travellers whose adventurous streak stretches to exploring space, so the chapter on space tourism may well be considered as the future in travel health.

Knowledge of all the above and other aspects of travel health and medicine are, therefore, an essential requirement for the many healthcare professionals providing advice and clinical care of the traveller. This is, however, dependent on understanding the science, which defines the practice, and the chapter on epidemiology and surveillance and the epidemiology of health risks and travel should be useful in underpinning best clinical practice in travel medicine. The recent European outbreak of measles is a case in point, which then informed the appropriate travel health vaccine recommendations. The desire to travel will undoubtedly continue unabated and will expand the minds of ever-increasing numbers of travellers. Lest we forget, the new chapter 'Tourism, aviation and its impact on travel medicine' acts as a timely reminder of how travel and tourism of whatever sort, are ever closely intertwined with health.

I am grateful to many friends and colleagues, who have contributed so willingly and enthusiastically to this book, through which we hope to stimulate healthcare professionals to consider issues in travel medicine as part of their clinical practice. I also hope that this reference book will enhance the profile of travel medicine and contribute to its continuing development as a distinct specialty.

I would also like to express my sincere gratitude to the editorial and production staff of Wiley-Blackwell, in particular Kate Newell and Maria Khan, for their patience and unwavering support.

Finally, this book is dedicated to my mother, who still speaks through me, and without whom I would not be the person I am today, and my father, who inspired me to complete the two editions of the *Principles and Practice of Travel Medicine*, and who is stalwart in his support. I am particularly indebted to my husband for always being there for me as well as always encouraging me, and to Iris, who has been more than a cousin and is like a sister to me. This second edition of the book would never have been realised without you all.

'Like all great travellers, I have seen more than I remember, and remember more than I have seen.' Benjamin Disraeli

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Section I
Travel medicine

Chapter 1 Trends in travel

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Introduction

'The great affair is to move.' The history of mankind is one of migration as humans travelled in search of food, escaping inhospitable climactic conditions, and in response to hardships caused by war, famine, social injustice and poverty. In the nineteenth and early twentieth century alone, 60 million people left Europe to seek better lives and to avoid the hardships of war. The health effects of these mass migrations are well known and include epidemics of infectious diseases, physical and psychological trauma, malnutrition and the introduction of diseases into new populations. Regrettably, such forced migrations are still a reality, as recent events in Africa, the Middle East and western Asia demonstrate. The types and severity of health problems seen in migrant populations are far different to those associated with tourism, the focus of this chapter.

In contrast to migration, which usually takes place out of necessity, tourism has become much more common and is associated with much different health risks to those seen in migrant populations. Humans have always yearned to expand their horizons by travelling. During the past 60 years, the explosion in tourism has created new economies in both developed and underdeveloped countries, created tremendous life experiences for millions of travellers and spawned a new branch of medicine.

Growth of tourism

Figure 1.1 depicts the dramatic increase in international travel since 1950. In that year, approximately 25 million people travelled abroad as tourists. By the year 2010, the number of international tourist arrivals will approach one billion; estimates are that nearly 8% of the world's population will travel to another country [1]. This impressive growth in international tourism has been approximately 8% per year since 1950. The growth has many causes:

- improvements in transportation
- changing world economies
- increased political stability
- the development of tourism as an industry
- increases in travel for health and education.

The growth of the commercial airline industry in the 1950s, and later the use of jet travel, have been cornerstones of the expansion of international tourism. As the relative cost of air travel has decreased and the ease of arranging flights has improved, this trend continues to drive increases in tourism. Just over half of all international tourists arrive by air. Highway and rail systems have also improved, particularly in Europe and Asia, and although only 3% of tourists arrive by train, roughly 40% reach their destination by car or bus. Only 6% of international travel is currently by boat [1].

Globalisation and improvements in the world economy have obviously been important in tourism. Increases in wealth in both industrialised and developing countries, in part driven by the tourism industry itself, are instrumental in the increase in international travel. Also important is an ageing population with increases in both wealth and leisure time. An important sector of tourism has been the population of migrants in industrialised countries who have had increased prosperity and who return to developing countries to visit families. This type of tourism is especially important for practitioners of travel medicine [2].

Improvements in political stability have also enhanced the opportunities for international travel. The disintegration of the former Soviet Union and the creation of the European Union are two obvious examples of changes resulting in increased opportunities for both business and leisure travel [3].

The rapid expansion of the tourism industry itself, especially in developing countries, has fuelled export income, which currently stands at more than US$1 trillion per year, or

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Figure 1.1 International tourist arrivals, 1950–2005 [1].

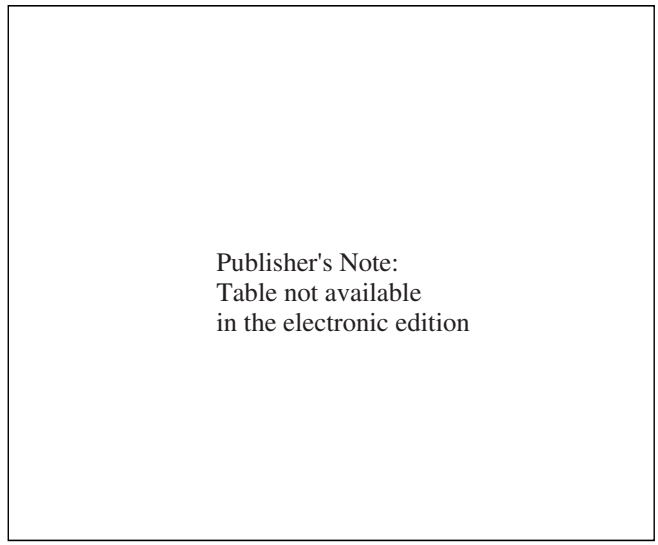
nearly US$3 billion per day [1]. The development of the tourism industry, with its great use of the nternet and advertising strategies, has been important in the expansion of tourism.

Finally, individuals are increasingly travelling for business, health and education. It was hard to imagine even a decade ago that patients from North America would travel to developing countries for surgery and medical treatment that is less expensive than in their own country. The impressive numbers of students who study abroad is of particular interest to the field of emporiatrics.

Where are international tourists going?

Most international tourism is for pleasure and is local; intraregional tourism accounts for nearly 80% of all international arrivals [1]. Moreover, the top destinations of international tourists, listed in Table 1.1, are mostly developed countries in Europe. In fact, Europe has nearly one-half of all international arrivals, although Asia, the Middle East and Africa have seen significant growth in the past 15 years (Figures 1.2 and 1.3). Since 1995, international arrivals to Asia, the Pacific and Africa have tripled, while during the same period arrivals to Europe and the Americas showed only modest growth. In addition, most international tourists visiting the Americas arrive in the United States or Canada. However, the fastest growing area in the region is Central America, which is certainly of more interest to practitioners of travel medicine [1]. Examining destinations of international travel in different regions, several patterns emerge.

- In the Americas, most travel is 'north–south' to Canada, Mexico and the Caribbean. Visitors from the US are much more likely to go to the Caribbean than South America or Central America.



- A French tourist is 20 times more likely to go to Africa than an American traveller.
- Twice as many English tourists visit India and Pakistan as American visitors.
- Australian tourists commonly have exotic destinations in Africa and Southern Asia.

Outbound tourism

Most international travel originates in developed countries, more than half of them in Europe (Figure 1.4). Asia and the Pacific have overtaken the Americas as the second most common origin for travel. In fact, emerging countries with rising levels of prosperity have showed higher growth rates

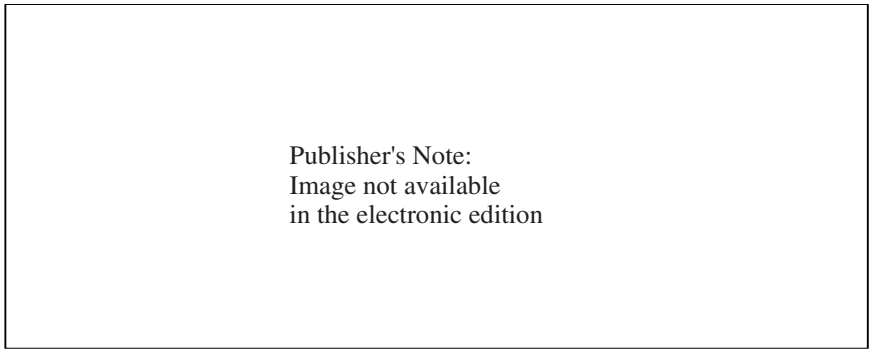


Figure 1.2 International arrivals (millions) by selected area (adapted from [1]).

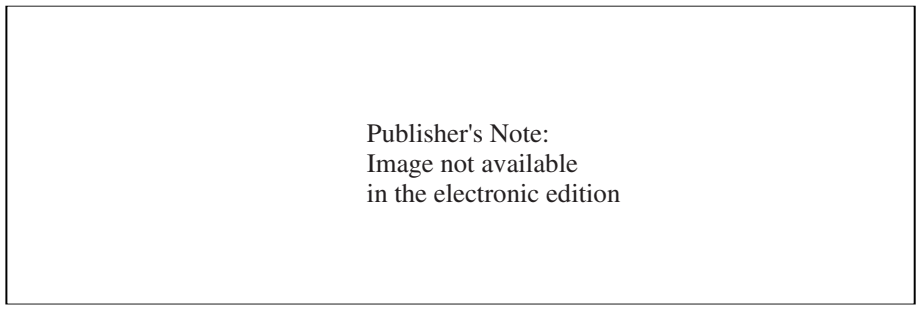


Figure 1.3 International arrivals (2008) by selected region (adapted from [1]).

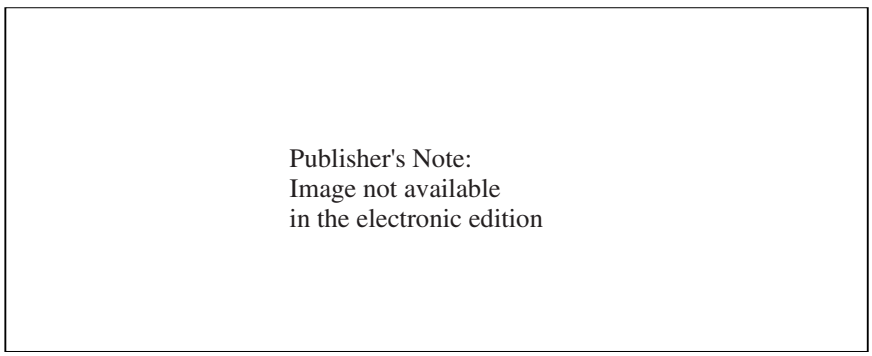


Figure 1.4 Outbound tourism, 2008, millions [1].

than developed countries as markets for the travel industry. This is especially true for northeast and southern Asia, Eastern Europe, and the Middle East. Although intraregional travel still dominates, interregional trips have grown twice as fast in recent years [1].

The economics of tourism

The importance of tourism as a driver of world economy cannot be overstated. Although lists containing the world's top tourism spenders and countries with the largest tourism receipts are nearly all developed nations, the relative importance of tourism to developing countries is much greater (Figure 1.5, Table 1.2). Currently, international tourism generates more than US$1 trillion per year and accounts for nearly one-third of the world's exports of commercial services. Perhaps more importantly, tourism is the leading export category for most developing countries. In these countries, tourism creates not only jobs, but much needed infrastructure. Currently, more than 80 countries earned US$1 billion or more. Examining the list of top

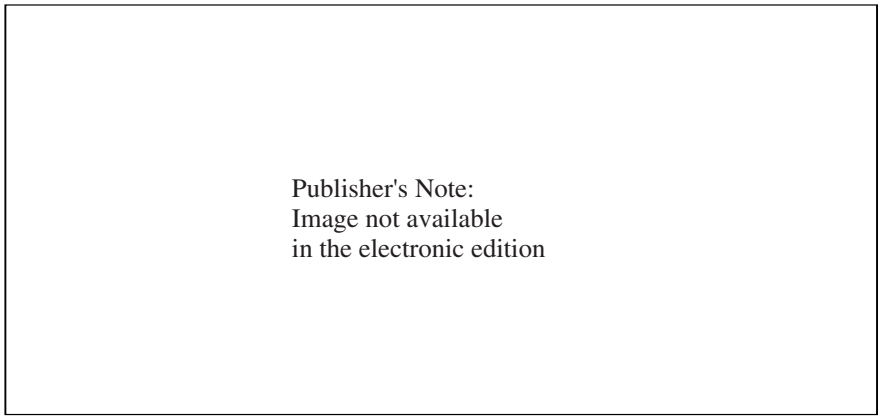
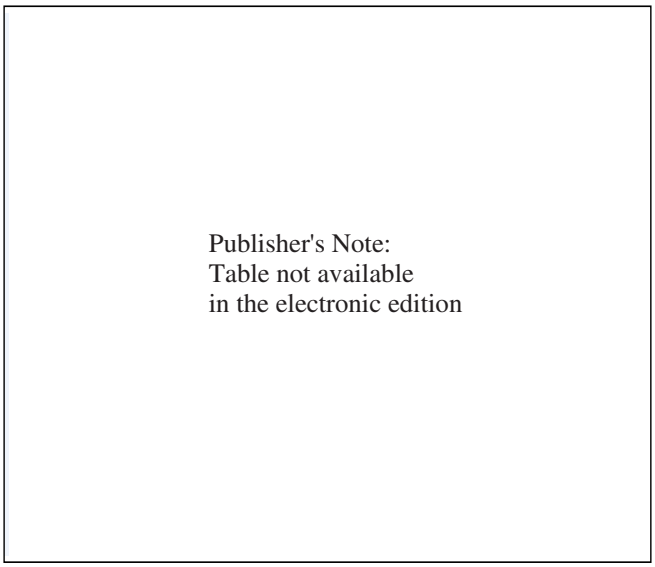


Figure 1.5 International tourist receipts (US$ billion) [1].



spenders (Table 1.3) in international tourism one learns that tourists from the United Kingdom spend nearly as much on foreign travel as travellers from the US; Germans spend more.

Trends in travel types

Although all travel has health risks, the healthy English family on a short holiday to France is of little interest to practitioners of travel medicine. The vast majority of international arrivals involve business or pleasure trips in developed countries. In addition, pleasure travel to less developed countries is often tour- or resort-based. However, there are trends in travel that are of more interest and importance for travel medicine:

- an ageing population
- increases in ecotourism
- students abroad
- visiting friends and relatives in developing countries.

We are currently witnessing the retirement of the wealthiest, healthiest and largest group of elders in human history. In the US alone, nearly one-quarter of the population is above 55 years old, and by the year 2030, there will be more than

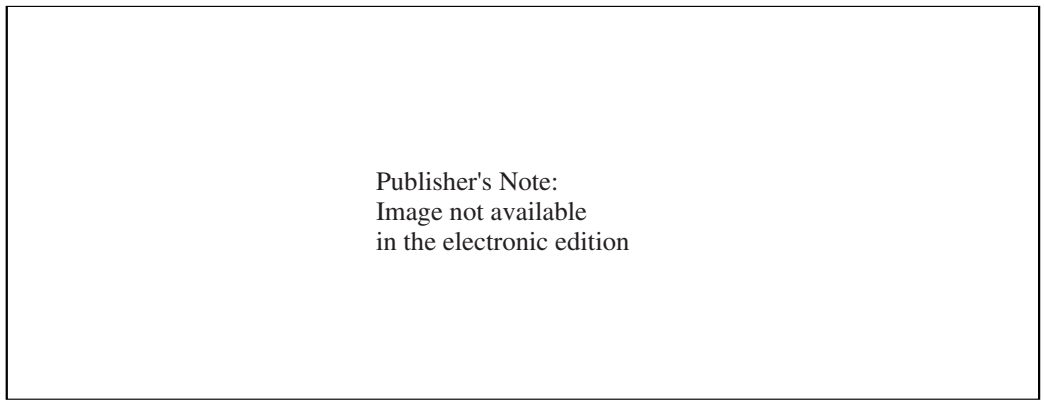


Figure 1.6 International tourist arrivals by purpose of visit (adapted from [1]).

70 million individuals above 65 years old. This population yearns for travel, and increasingly exotic travel. Preparing elders for trips presents challenges to healthcare practitioners and for those interested in expanding infrastructure for tourism. Health risks are clearly greater. A recent study found that of more than 2,400 deaths in Canadian travellers, the average age was 62 and most died of natural causes [4].

An increasingly popular type of travel is ecotourism. This type of adventure travel is often to poorly developed areas in the tropics, with potential exposures to excessive sunlight, vector-borne diseases, and contaminated food and water.

Another trend is the increase in students studying and working abroad. The number of US students abroad has doubled in the past decade to more than a quarter of a million per year. Most of these students have destinations in developed countries, but nearly 20,000 US students study in Mexico and Central America. Many students also spend time working as volunteers in rural and underdeveloped countries, usually working for non-profit organisations. As opposed to short-term tourism, students typically stay for longer periods, take greater risks than older travellers and often have ill-defined itineraries.

Visiting friends and relatives (VFR) is a rapidly increasing reason for international travel (Figure 1.6) and of special interest to emporiatrics [2]. In the US alone, one-fifth of the population (56 million people) are foreign-born or their US-born children. Overall, about a quarter of all international arrivals are VFR travellers, but 44% of trips abroad from the US, excluding travel to Canada and Mexico, are currently for this reason. Most of these travellers are returning to developing countries, half to Latin America and a quarter to Asia. The five top countries for legal immigrants in the US are currently Mexico, India, China, the Philippines and Vietnam.

As a group, VFR travellers are much more likely to acquire illness abroad than other types of tourist. They are usually visiting less-developed countries, staying in crowded conditions, staying longer, and more likely to be exposed to contaminated food and water. Compared to travellers for business and leisure, VFR travellers are less likely to be insured or to seek pre-travel advice. The immunisation status of VFR travellers is often incomplete and uncertain. They often bring their US-born children who have no immunity to malaria, and often sleep without protection from mosquitoes. In the past 15 years, most of the cases of falciparum malaria and all of the cases of typhoid fever seen by our travel clinic were children of immigrants returning from visits abroad. As immigrant populations in the US expand and mature economically, VFR travellers are certain to increase.

Future trends

'It's tough to make predictions, especially about the future' (Yogi Berra). By the year 2020, international arrivals are expected to reach 1.6 billion (Figure 1.1). The economic forces that have made tourism so important for developing countries – improvement in infrastructures, the internet and an expanding population of persons yearning to travel – are some of the many reasons for this expected continued growth. However, after years of steady growth in tourism, there have been recent worldwide decreases in both tourist arrivals and receipts. The major factor in the recent downturn is obviously worldwide economic recession, but other factors include rising fuel prices, unstable and unfavourable currency exchanges, and even fear of epidemics (influenza). Social and political unrest may also have negative effects, although the region with the most robust growth in recent years, the Middle East, is one of the most volatile (Figure 1.2). Of theoretical concern is the impact of global warming and its relationship to air travel.

References

1. WTO (2009) *World Tourism Highlights*, 2009 edn. World Tourism Organization, Madrid; http://www.unwto.org (accessed 11 September 2012).
2. Angell SY and Cetron MS (2005) Health disparities among travelers visiting friends and relatives abroad. *Annals of Internal Medicine* **142**: 67–73.
3. Handszuh H and Waters SR (1997) Travel and tourism patterns. In: DuPont HL and Steffen R (eds) *Textbook of Travel Medicine and Health*, pp. 20–26. BC Decker, Ontario.
4. MacPherson DW *et al.* (2007) Death and international travel – the Canadian experience. *Journal of Travel Medicine* **14**: 77–84.

Chapter 2 Tourism, aviation and the impact on travel medicine

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Introduction

International tourism demand has grown very considerably over the past few decades. According to the United Nations World Tourism Organization (UNWTO), international tourist arrivals have risen from just 166 million in 1970 to more than 922 million in 2008. Likewise, tourist spending has increased from US$18 billion to US$944 billion. The majority of tourism visits are for leisure, recreation and holiday purposes (51% of all visits in 2008) with 15% for business and a further 27% for visiting friends and relatives (VFR), health, religion and 'other'. While demand is forecast to be weak in the short term due to the poor economic climate, in the longer term the UNWTO expects healthy growth to return and numbers to reach 1,561 million by 2020 [1]. The World Tourism and Travel Council (WTTC) has also forecast that the travel and tourism economy will grow by 4% per annum in real terms over the next 10 years and will then account for a very significant 275 million jobs or 8.4% of total global employment [2].

Transport is a fundamental component of tourism, providing the vital link between the tourist-generating areas and destinations. Aviation is an increasingly important mode of transport for tourism markets and currently 52% of all international tourists arrive by air (Table 2.1). While geography has meant that, in modern times, air travel has always been the dominant mode for long-distance travel, trends towards airline deregulation, and the subsequent emergence of the low-cost carrier (LCC) sector, have also increased aviation's significance for short- and medium-haul tourism trips.

Travel medicine meets the health and safety needs of these tourists and air passengers who are going to a variety of destinations and for a range of different purposes. It has evolved from being considered just a component of infectious, topical and preventive medicine to becoming a recognised interdisciplinary specialty that has a wide range of contributions from both physical and social science. Epidemiology, accident and emergency medicine, safety science and ergonomics, tourism studies, management, food safety, leisure studies, law, social psychology, tropical medicine and health education are examples of just some of the subjects that have contributed to the development of travel medicine [3].

It is the aim of this chapter to bring together these topics of travel and medicine and to investigate the impact of tourism and aviation trends on travel medicine. This will be undertaken by first identifying the various links and interrelationships between tourism and travel medicine. This leads on to an assessment of the changing patterns and types of tourism. This then allows the impact of tourism developments on travel medicine to be explored, which is followed by an examination of the effect of airline trends. Finally, conclusions are drawn.

The relationship between tourism and travel medicine

The rise in tourism demand and the rapidly growing mobile population has meant that the health and safety of tourists has become an increasingly important and complex issue. However, it is not just the volume of tourism that is changing, it is also the characteristics of the tourists and their trips. The multidimensional discipline of travel medicine has developed to cope with these changes by covering an increasingly diverse range of travel-related health areas, such as guidance about sun-seeking and sexual behaviour, malaria prevention, and advice related to injuries and accidents [4]. As a result there have also been an increasing number of detailed travel medicine manuals that aim to provide comprehensive coverage of all aspects of travel medicine [5, 6].

Travel medicine has to be considered at all stages of the trip, namely the pre-travel planning stage, the journey to and from the destination, the stay at the destination, and

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Table 2.1 International tourist arrivals by mode of transport 1990–2008 (%)

	1990	2000	2005	2006	2007	2008
Air	39	42	45	46	47	52
Road	47	45	43	43	42	39
Rail	6	5	5	4	4	3
Water	8	8	7	7	7	6
Total	100	100	100	100	100	100

Source: UNWTO

post-travel follow-up and aftercare. At all times during their trip, tourists are exposed to risk. However, the scale and probability of these risks will vary from rare cases of tourist mortality, for example associated with deep vein thrombosis (DVT), to more frequent but still comparatively unusual cases of malaria and other disease infection or road traffic accidents, to minor but common problems associated with small injuries, diarrhoea and sunburn [3]. The psychological and behavioural aspects of travel associated with issues such as fear of flying, trauma and stress also need to be considered as well as special needs of certain groups of tourists, such as the elderly, and any underlying medical conditions that exist.

Clearly the increased movements of people across political and physical borders can have a number of unwanted consequences for health, particularly as disease knows no frontiers. Recent examples include the Severe Acute Respiratory Syndrome (SARS) and A(H1N1) 'swine' flu that were spread rapidly and globally by the movement of tourists. In some cases disease may be spread from a remote region to other areas where it is not so familiar and hence it will be more difficult to implement biosecurity and coping strategies.

However, not only does travel have major impacts for health, but also the risks associated with travel have important implications for health and tourism services. Moreover, the inter-relationship between travel and health can have very significant consequences for the insurance industry and legal sector when issues of litigation may become relevant. In terms of the provision of health services, there are numerous examples of where destination countries have benefited from better accident and emergency facilities, and improved cleanliness and hygienic conditions as a result of bringing tourism to the area. Likewise, drugs and vaccines that are initially developed for tourists at a high price, often eventually become more widely available at a significantly lower cost.

For the tourism industry, ensuring that the tourist is in good health and is safe is now a crucially important aspect of any operation. The industry also has a role to inform potential tourists of the risks involved. The composite nature of the tourism industry, being made up of a number of individual sectors (e.g. transport, hospitality, attractions, tour operations, travel agency, destination organisations) in both public and private ownership makes this process more difficult. In particular, it makes it problematic to define and identify the individual sector responsibilities to safeguard the health of tourists and to ensure that the advice and information that is being provided is entirely consistent.

The industry is only too aware of the commercial implications (e.g. on tourism volume and sales) of overplaying the potential risks and so here a careful balance has to be found. Labelling a country as high risk for a disease may have serious economic consequences for both the industry and the destination. For example, Figure 2.1 shows the impact that SARS, which was most prevalent in Asia, had on tourism numbers in 2003. Some countries such as Hong Kong experienced a 70% drop in their tourism numbers. The only other region to have experienced a decline in tourism numbers was the Americas, primarily due to 9/11 (and SARS outbreaks in Canada). More recently, between May and July 2009 in Mexico, where the first cases of the swine flu outbreak were recorded in April of that year, 2,000 inbound flights were cancelled and Mexico was estimated to have lost between US$200 and US$300 million in tourism income. Overall in 2009 it was expected that arrivals and spending would be down by a third [7]. Communication with the media can be crucially important here as it is often press messages that will act as the most influential trigger in changing tourists' perception of a destination.

The nature of products that the industry offers, in terms of type and location of destination, mode of transport and type of accommodation, will have a major influence on the risks to which the tourist is exposed. In addition, the amount of contact with the local inhabitants may have an impact. An obvious example is the tourist who chooses to stay in a resort or go on a group tour where the health risks can be more easily managed, compared with one who is seeking greater exposure to the indigenous population and participating in more individual activities where the risks are likely to be greater. In some cases companies may choose products where the risk factors can be better controlled, as with 'enclave' or 'all-inclusive' resorts in lesser-developed countries. Seasonality and length of stay will also have an impact, as will the purpose of travel. For example, the risks associated with business tourists will usually be perceived as smaller than for other tourists because the majority of these trips are to towns or cities where the visit is spent in a hotel and/or conference centre of a relatively high standard. The exception to this is when it is considered essential to maintain

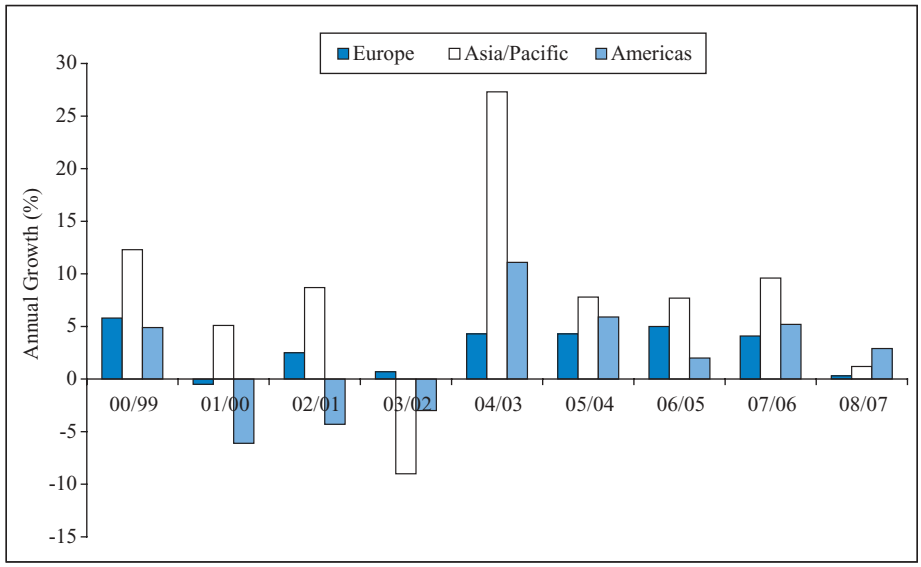

Figure 2.1 Annual growth rate of international tourist arrivals by major world regions 1999–2008 (%).
Source: UNWTO

business contact by making a trip to a country where the health or safety risks for leisure travel are seen to be too high.

Some of the risks will be more specific to the individual tourist, related to their age, medical history and fitness to travel. Other factors include their experience of travel and whether they are frequent or infrequent travellers. A very important aspect is also the behaviour and lifestyle of the tourist. For example, some tourists choose to take more risks when they are away from home and perhaps ignore advice that has been given. Others may travel specifically because of the excitement of the risks that the travel experience brings. In most cases the risks will be highest when the tourists are exposed to new hazards that they have previously not encountered.

Changing patterns and types of tourism

The evolution of tourism through the ages has continually led to changes in the patterns and types of tourist. This is just as evident today as it has been in the past. In particular, one of the most notable developments in recent years has been a shift in the global distribution of tourism, with the dominant markets of Europe and America reducing their market share of arrivals from 82% to 73% since 1990. This is partly due to increased travel within other more developing regions, particularly in Asia/Pacific, because of rising living standards and a more liberal air transport environment, which has given many the opportunity to travel by air for the first time. It is also in part because of the development of long-haul travel, particularly from Europe and North America to other regions. This has been driven by economic deregulation and globalisation, which has encouraged greater mobility of businesses and led to more international business travel, and for leisure travel due to cheaper costs and changing consumer preferences and motivations.

This increase in long-haul travel may clearly be seen from Table 2.2. Since 1990 there has been higher growth in interregional rather than intraregional travel except during the period between 2000 and 2005 when long-haul travel was deterred primarily as a result of 9/11 and SARS. Moreover, the share in international tourist arrivals received by developing countries has steadily risen, from 31% in 1990 to 45% in 2008. This trend is forecast to continue into the future with the UNWTO predicting that long-haul travel will grow at 5.4% per annum until 2020 compared with 3.8% for intraregional travel [1].

In many Western societies there have been significant changes in family structure, life stage and lifestyle that have affected tourism. For example, there is a tendency to marry later in life and have smaller families at an older age. As this is occurring at the same time as more couples are opting to remain childless, it means that there are a rising number of young couples travelling, who have fewer income and time constraints than families with children. There are also higher divorce rates and a growing number of singles and one-parent families who are travelling.

Another key development has been the growth of the so-called 'grey', 'third age', 'mature', 'senior' or over-55s market

Table 2.2 Average annual growth rate of international tourist arrivals by origin region 1990–2008 (%)

	1995/90	2000/95	2005/00	2006/05	2007/06	2008/07
Same region	4.1	4.6	3.4	5.5	6.0	1.8
Other regions	4.5	6.4	2.6	7.3	8.1	3.4
Overall	4.2	4.9	3.2	5.9	6.4	2.1

Source: UNWTO

Table 2.3 Examples of tourism trends 1997–2008

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
International trips by UK residents												
Trips by residents >55 years (%)	17	18	20	20	20	21	22	23	24	25	24	24
Air package tours/total air holiday trips (%)	61	60	59	59	57	55	50	48	45	42	42	40
Travel sales in Europe												
Internet/Total sales (%)	0	0	0	1	2	4	7	10	13	16	19	23

Sources: UK International Passenger Survey, Danish Centre for Regional and Tourism Research

[8]. This age group is becoming proportionately more important within the population due to people living longer and birth rates falling in Western economies such as Europe and North America. The propensity to travel of this age group has also increased, not only because this market segment has plenty of time to travel, but also because such travellers are wealthier, healthier and more experienced than before. Moreover, there is less of an expectation that their savings should be left to their offspring and a greater acceptance that such funds should be used for pursuing leisure activities in later life. Table 2.3 shows how in the UK the share of international holidays taken by the over-55s has increased from 17% in 1997 to 24% in 2008.

At the other end of the age spectrum there are youth travellers. This market has been steadily growing due to a number of demand-related factors such as increased participation in higher education, falling levels of youth unemployment, and increased travel budgets through parental contributions, savings and combining work and travel. There are also supply side factors that have encouraged this such as the rise of LCCs, growth in long-distance travel specifically targeted at young travellers, shorter employment contracts for those working leading to significant gaps in employment, and the growth of dedicated student and independent travel suppliers [9].

Among this youth market there has been a very significant increase in those who are studying and travelling abroad. For example, in 2004 more than 2.4 million students pursued higher education outside their home country and it has been estimated that this will increase threefold to eight million by 2025 [10]. In addition, there have been a growing number of young travellers who are taking gap years either before or after they study. However, the taking of gap years is not now just considered a youth phenomenon, as it used to be. There has been a growth in adults taking a diverse range of gap activities, for example with their families, in between careers or at retirement age – albeit the numbers involved are still quite small. This has led to terms such as 'career gappers', 'golden gapper', 'twilight gapper', 'mature gapper' or 'denture venturers' [11]. There has also been a growth in travelling to undertake volunteer work – the so-called 'give back gap'.

For many, attitudes to travel are changing and tourists are becoming more sophisticated and demanding. This is occurring as travellers are becoming more experienced and better educated. There is a heightened awareness in foreign culture and there are an increasing number of publications, both books and magazines, about travel. Moreover, travel marketing has improved, particularly with the use of the internet. This means that travellers are more adventurous and often more environmentally and ethically aware. In addition, many travellers are expecting their holiday experience to be more personalised and to be more related to their individual lifestyle and choice.

This has resulted in a marked broadening of the range of requirements for the holiday product. Companies are increasingly expected to demonstrate that they are encouraging 'responsible' travel and there are an expanding number of 'nature', 'green' or 'eco'-tourism products on offer. This has also meant that there has been a growth in demand for diverse adventure activities such as mountaineering, white-water rafting, hiking, sailing, rock climbing, recreational diving and mountain climbing [12]. Moreover, there is a rising demand for more extreme and strenuous sports such as BASE jumping, canyoning, coasteering/tombstoning and speedriding, and new adventure destinations such as Georgia, Kyrgyzstan, Ethiopia and Libya [13].

One of the ultimate types of adventure is being offered by the embryonic space tourism industry. Four main kinds of space tourism, namely high-altitude jet fighter flights, atmosphere zero-gravity flights, short-duration sub-orbital flights and longer-duration orbital trips, may become available in the near future. There have already been several fare-paying tourists visiting the International Space Station via the Russian Soyuz spacecraft and the company involved with organising this, Space Adventures, has more than 200 people prepared to pay the $100,000 for a 90-minute sub-orbital flight. Likewise, Richard Branson's initiative Virgin Galactic has sold $200,000 flights to 100 individuals [14].

Another trend is that tourists are demanding greater flexibility, which is reflected in the trend towards holidays of different and shorter duration, rather than the traditional two-week break. Some of this growth has been fuelled by the development of the LCC sector, which has made it possible for many to afford a weekend break away, particularly in Europe. This has encouraged the growth in activities such as hen and stag weekends, festivals and beach parties, and the development of European nightlife resorts such as Kavos, Zante, Malia, Magaluf and Ayia Napa.

This need for flexibility has also caused a shift towards independent travel rather than organised package holidays and a considerable growth in dynamic packaging, where tourists construct their own individual package tour. For example in the UK, Table 2.3 shows that package tours by air taken by UK residents now account for around 40% of all international holidays compared with 60% just 10 years ago. Travellers are also making their travel arrangements much later than previously. Much of this flexibility has come from the development of the internet as a major distribution channel for travel products. Indeed in Europe, internet travel sales now account for around a quarter of all sales (Table 2.3). In many cases this means that the high street travel agent intermediary is by-passed.

The desire for spiritual and physical wellbeing is also causing a growth in a number of specialist tourism areas. First there has been a rise in religious or pilgrimage travel, with visits to a religious place, building or shrine or to a religious event [15]. The largest and most well known of these movements is Hajj, where in 2008, 1.7 million visitors from 178 countries travelled to Mecca, compared with around just one million only 10 years previously. Other tourists are travelling for mental and physical wellbeing, and there has been a growth of holidays where tourists are seeking therapies and treatments and pursing activities such as yoga and spa holidays. Another growth area is medical tourism, where travellers visit countries where the cost of surgery or dentistry is considerably lower than in their own country, for example for coronary bypass in India or breast augmentation in Cuba. The size of this overall market is hard to estimate, but in the UK, health and wellness holidays have been valued at £64 million, compared with £90 million for medical tourism. However, this activity is still comparatively small and in a survey, only 1% of UK adults said that they had had medical treatment abroad in the past three years – which would be equivalent to 700,000 trips [16]. In spite of this niche market status, for certain destinations medical tourism can be significant. For example in India it is expected to be worth $1 billion by 2012 and 3–5% of expenditure on healthcare will be related to medical tourism[17]. One notable example of the development of this type of tourism is 'Healthcare City' in Dubai, which is a huge complex that is being developed to become an international centre for both medical and wellness services.

The impact of tourism trends on travel medicine

Travel medicine is having to adapt to these changing patterns and types of tourism. This means taking account of the demand segments that are showing the most growth and the types of product that are rising in popularity. There also has to be consideration of other trends, such as greater flexibility and changing booking habits.

All the changes in family structure, life stage and lifestyle that have been discussed will undoubtedly have some impact on travel medicine. For example, the growth in singles travelling may present greater risks and anxieties in some cases. With senior travel, there is still a popular perception that this market consists of frail old people walking round with walking sticks. This is totally incorrect, especially as these travellers represent a number of diverse and heterogeneous groups. In relation to health, these travellers can be divided into the health optimist (those in good health), the travel recipient (those with pre-existing health complications) and the carer (those who have to care for others) [18]. Each segment has different travel medicine needs, although it is the case that the impact of any illness tends to be more

serious for this age group, particularly if there are underlying medical conditions.

Youth tourism brings other challenges. While this market segment will generally be healthier, these travellers are often those who are prepared to take more risks. This is no doubt related to age, but it may also partly be explained by the fact that such tourists will often be very cost conscious and travelling on tight budgets, and so believe that they cannot afford to avoid the risks if it costs them money to do so. Moreover, an increase in more hedonistic activities with this age group, associated with the enjoyment of alcohol at hen and stag trips and recreational drug use at music festival and resorts, has brought with it behavioural issues related to sexual conduct, violence and crime, which have to be addressed.

The trend towards greater long-haul travel, and in particular to lesser-developed countries in tropic and sub-tropic regions, has given tourists greater exposure to a different health environment. For example, they may experience significant changes in temperature, altitude and humidity that may affect their health. There may also be increased risks of venomous bites and stings and catching malaria. In addition, the lower quality of accommodation and poorer standards of hygiene and sanitation that can exist in such areas may increase the health risks, particularly if the medical services are not very well developed.

For many tourists, one of the key motivations for travel is the desire for new experiences. This exposure to unfamiliar surroundings will create some risks, but these can usually be managed. However, the growth in adventure tourism has presented new challenges in the field of travel medicine as these activities are based on an experience that involves considerably more inherent physical risks to the traveller. If the risk were to be reduced, so would the thrill and excitement of the experience. This is true of most adventure travel, but particularly with the new concept of space tourism, the travel medicine implications are very difficult to predict.

Mass religious gatherings present considerable challenges for travel medicine due to health and safety risks, because of accidents and even loss of life as the result of overcrowding, and health concerns of having such a large concentration of people that could encourage a fertile breeding ground for germs. For example, at the Hajj, there have been a number of deaths due to stampedes and inadequate crowd control in recent years. This has led to the Saudi government making improvements to security and certain facilities, and extending the access hours to religious sites. Moreover, after outbreaks of meningitis in 1987 and 2000–01, it is now a visa requirement that pilgrims going to Mecca have received the meningococcal meningitis vaccination.

The emergence of medical tourism has brought its own risks. For example, where surgery does not go to plan and tourists have to seek medical assistance, either at the destination or when they return home.

Other tourism trends can potentially have significant impacts on travel medicine. The preference for booking later may mean that tourists do not have time to seek all the travel advice they need or to have all the required immunisations and vaccinations before they leave for their destination. Also, buying the components of travel (e.g. flight, accommodation) separately rather through a tour operator means that there is no longer one major central source of information and advice related to the trip that is being undertaken. With less use of travel agents, another channel of advice is also no longer available to an increasing number of tourists.

The growing use of the internet for obtaining travel information and booking trips has a number of potential impacts on travel medicine, particularly on pre-travel advice. It makes it easier to provide up-to-date government advice to a broad audience on countries that should not be visited or are at high risk. Likewise, official health authorities can centralise their advice and rapidly update it when necessary. However, such information, as with all advice given on the internet, may not have as strong an influence as face-to-face help.

There has been a significant rise of media interest in travel, and in particular in negative events, and this has led to considerable variability in the advice offered on the internet. On the other hand, it does provide greater opportunities for potential tourists to weigh up the costs of reducing the potential risks, for example with the side effects of the drugs associated with preventing malaria. However, the sheer quantity of pre-travel advice now provided on the internet might be unmanageable for some people. In reality, much travel advice is and will remain anecdotal, but there are new ways of communicating this, particularly for young travellers, with blogs, wikis and other social networks.

The impact of aviation trends on travel medicine

The emphasis so far has been on health precautions prior to departure and problems encountered at the destination. However, the actual journey to and from the destination raises a number of additional issues related to travel medicine. While consideration needs to be given to all modes of transport, the unique characteristics of air travel and its growing importance within tourism mean that this mode is particularly important and hence has received special focus here.

Forecasts for air transport demand mirror those produced for the tourism industry. Passenger numbers are predicted to increase by an average 4.2% annually, which will mean

Table 2.4 Past and future airport passenger growth by world region 1999–2027

	1999 (mns)	2007 (mns)	2027 (mns)	2007 market share (%)	2027 market share (%)	Forecast annual growth 2007–2027 (%)
Africa	60	138	401	2.9	3.6	5.5
Asia	450	1,150	3,918	24.0	35.7	6.3
Europe	901	1,472	2,868	30.7	26.1	3.4
Latin America/Caribbean	120	328	869	6.8	7.9	5.0
Middle East	60	158	387	3.3	3.5	4.6
North America	1,411	1,552	2,536	32.3	23.1	2.5
World	3,003	4,798	10,976	100	100	4.2

Source: ACI

that by 2027 there will be 11 billion passengers or 30 million passengers per day. Again growth is predicted to be highest in areas outside Europe and North America, and in particular by 2017 the Asia/Pacific region will be the busiest air transport area [19] (Table 2.4). Boeing is predicting an average annual growth rate until 2028 in passenger-kilometres of 6.7% between North America and Southeast Asia, 6% between North Americaand China, and 5.7% between Europe and Southeast Asia and China, compared with an average of 4.9%. Forecasts for traffic to and from the Middle Eastern and African regions are also higher than the norm [20].

The propensity to travel by air varies considerably throughout the world. Australia has 5.6 passengers per head of population followed by the United States with a value of 4.7. At the other extreme Russia and Brazil have values of 0.6, China 0.3 and India 0.1. Even within Europe there is a broad variety of values, with island countries, such as Cyprus, and countries with remote regions, such as Norway, already having values greater than 6, whilsepoorer countries, such as Albania and Macedonia, have measures substantially lower than 1 [21]. There is thus considerable scope for growth in these countries where propensity figures are still low, if and when economic and other conditions become attractive enough to generate and attract substantially more air passengers.

Aviation medicine is a wide-ranging component of travel medicine covering physical and psychological aspects of flying, such as the recognised conditions of motion sickness and fear of flying [22], as well as issues such as fitness to travel [23]. Moreover, the rising numbers of air passengers has meant that air travel has become increasingly complicated and considerably more stressful, which introduces more health implications for travellers [24]. This stress is related not only to the actual flight but also the pre-flight processes such as getting to the airport and going through all the airport processes.

The airport experience has changed as airports have had to become larger and more complex to cope with the increasing number of passengers. Services are provided on many floor levels and in different terminals, such as at London Heathrow airport, which now has five terminals. This means that there is very often a long distance between check-in and the boarding gates, and transferring between terminals when changing flights can involve a long and time-consuming journey. Passengers have to check in, be processed by security, customs and immigration authorities, and find their way to the gate for their aircraft – all of which can be stressful for passengers, particularly infrequent flyers who are unfamiliar with the airport. Enhanced security arrangements due to 9/11 and the liquids scare in 2005 have increased the burden of security checks. On average, international passengers spend 83 minutes in the airport terminal. Sixty-two minutes of the time is landside, with 23% on check-in, 16% on customs and immigration, and 12% on security, which illustrates just how much time has to be spent going through the essential airport processes [25]. Traffic growth means that congestion and longer queues in the terminal are likely. Moreover, more aircraft have to share air space, gates, runway capacity and parking, which again can increase congestion and delays. This is a major issue for the industry as there are currently 154 airports in the world where potential demand exceeds supply (in terms of runway capacity) and a further 83 where potential demand is approaching capacity [26].

Larger airports have, however, provided airport operators with the opportunity to offer a wider range of retail and food and beverage outlets that would not all be economically viable at smaller airports. For some passengers this shopping experience enables them to feel more relaxed and enhances

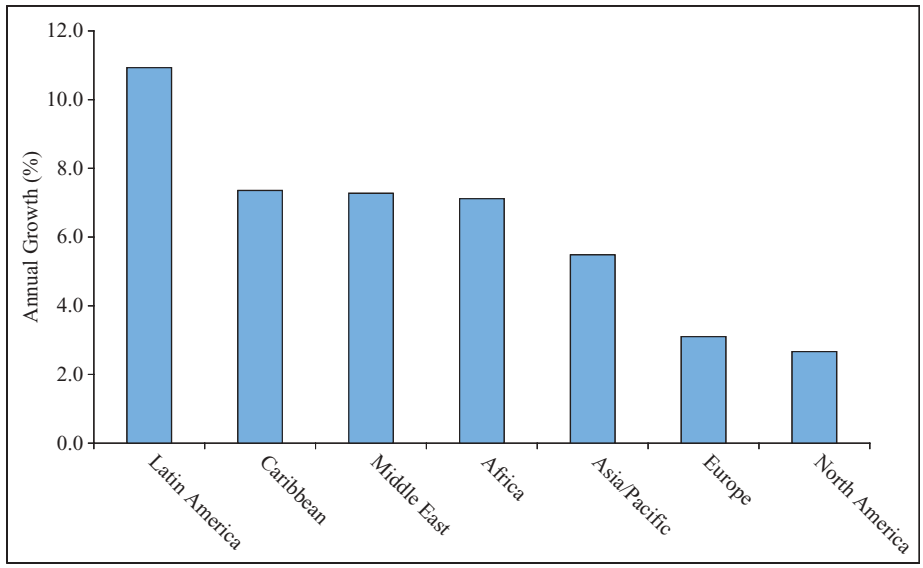

Figure 2.2 Growth in aircraft size by world region 1972–2008 (%).
Source: Airbus

their enjoyment of their airport visit and overall trip. Some airports have gone a stage further, providing passengers with relaxation activities. For example, Singapore Change airport offers a swimming pool, sauna, gym and cinema. On the other hand, for the growing number of passengers who have opted for a journey to a lesser-developed country destination, the airport facilities in such places may be more basic with more cumbersome immigration, customs and security controls, which can increase anxiety levels.

The stresses on board can also in part be related to the larger volume of passengers being flown in each aircraft. Over the years, the average aircraft has increased in size to cope with demand growth and to take advantage of the better economics that are available when flying larger aircraft. Certain regions with specific location characteristics and particularly strong growth have experienced the most notable increases in aircraft size. For example, Figure 2.2 shows that the Middle East and Asia/Pacific regions have encountered the greatest growth and the average number of seats here has increased from around 135 in 1972 to just under 190 in 2008 [27].

One of the most significant recent developments in terms of aircraft size has been the emergence of the world's largest aircraft, the Airbus A380. This came into service in 2007 and Airbus is predicting that 1,318 of these aircraft will be needed by 2028, particularly for Asia/Pacific (55% of total) and the Middle East (14% of total). While generally larger aircraft tend to mean that the service provided is more impersonal and introduce more scope for passenger and baggage delays because of the sheer volume being handled, the larger space in the A380 has provided an opportunity for some of carriers that use this aircraft (e.g. Singapore Airlines and Emirates) to offer improved comfort and in-flight services, particularly in the first and business cabins. With a three-cabin configuration the numbers of seats is around 550, but if only one class is chosen, as is the case with an order from Air Austral, 840 passengers can be carried, which will indeed be a different travel encounter yet to be experienced.

Since more people are flying long-haul, aircraft with longer ranges have been introduced, which has reduced the need to make stops for technical reasons. This tends to increase the medical problems associated with flying, and has led to airlines and other bodies having to pay more attention to publicising possible remedies for jet lag, which is caused by the body crossing different time zones [28]. The possibility of developing DVT is also an issue that has grown in importance and in some cases has encouraged airlines to introduce more comfort for long-haul flights, for example by increasing seat pitch. Another area of concern is the poorer quality of air, primarily due to the increase in the intake of reprocessed air in aircraft cabins, as a result of airlines trying to save fuel.

A more impersonal environment on board, due to the increased number of passengers, and boredom, particularly during long-haul flights, is thought to be playing some role in increasing disruptive behaviour among passengers, especially if they have consumed alcohol and are now unable to smoke. 'Air rage' has received considerable media attention in recent years and is something that airlines now have to face with increasing frequency [29].

Another very significant development over the past decade or so has been the emergence of the LCC sector. This has had a substantial impact on the growth in tourism, particularly in North America and Europe, but also in other areas such as Asia. These airlines typically have a number of characteristics that can have an impact on passenger stress, comfort and behaviour. At the airport these carriers favour simpler operations, with no air bridges or buses, which may cause some discomfort or irritation to passengers. They often choose to fly from small secondary airports, which will be favoured by some passengers because of their relative smallness, but not by others due to their remoteness. On board there is usually no seat allocation, high seating density, no free food or drink and a smaller number of cabin crew than with other airlines. There is an increasing tendency to charge for hold baggage, which is encouraging more passengers to travel with hand luggage only, which can add to the general discomfort on board. Significantly, a number of other airlines, having seen the success of the LCC sector, are also adopting some or all of these characteristics of the LCC model.

Other identified tourism trends are also having a varied impact on airline medicine. For example, with the growth in the senior market and their higher propensity to become ill, comes an increased need for airlines to provide repatriation services. The tightening up of security checks has meant that in some cases it is more difficult for passengers with underlying medical conditions to carry medicines on board. With more independent booking and less buying through travel agents and tour operators, advice about how to get to the airport, how long is needed to check in and so on is left entirely in the hands of the traveller, which may not always be very effective and can cause additional anxieties.

There is also increased interest in the exact role that air travel plays in spreading diseases [30, 31] and to what extent this can be influenced, for example by restricting air travel. The examples of SARS and swine flu demonstrated how quickly such diseases can be spread. Since airports are usually the first and last point of contact that a tourist will have with a destination, in many cases it is the airports that have had to take on the important role of screening passengers. Some airports have gone further than this and, for example, Frankfurt airport has the world's largest airport medical clinic. Moreover, the International Civil Aviation Organisation (ICAO) now provides the air transport industry with guidelines related to such screening as well as other issues related to the spread of diseases (e.g. communication, airport closure, flight restrictions, aircraft cleaning and handling), which is supplemented with information from industry organisations such as Airports Council International (ACI) and the International Air Transport Association (IATA) [32].

A further development that has the potential to spread diseases is airline hubbing. This is where airlines choose to operate hub and spoke operations, with many passengers transferring between planes at the hub to get to their final destination rather than taking direct flights. This means that more passengers come into contact with each other than would otherwise have been the case. The amount of transfer traffic has increased at a number of airports over the years, accounting for well over a third of traffic at European hubs such as Paris, Heathrow, Amsterdam and Frankfurt, and an even greater share at US airports such as Atlanta and Chicago.

Conclusions

The impact that travel medicine can have on travel patterns, for example by enabling passengers to travel safely to areas that were previously very risky, or by enabling them to fly without becoming ill, is reasonably well documented. However, the reverse situation, namely the impact that tourist and air passenger flows can have on travel medicine, is generally not so widely considered and hence this chapter has attempted to go some way towards filling this gap.

Issues of tourist health and safety are increasing in importance, with tourist wellbeing becoming a critical concept in relation to tourist satisfaction. Many people travel in order to relax on holiday and do not want to expose themselves to stresses and anxieties that will discourage this from happening. However, all risk can never be taken out of tourism or the experiences will cease to be exciting or fulfilling. The challenge, therefore, is to achieve a balance between meeting the needs of the increasingly sophisticated, experienced and individual tourist on the one hand, and a realistic assessment of the increasingly complex world of travel medicine.

As tourist and air passenger characteristics and preferences continue to evolve through time, so will their travel medicine needs. For example, long-haul travel is forecast to grow and could perhaps become the domain of LCCs. However, it could decrease because of high fuel prices or environmental concerns. Globalisation trends are predicted to further encourage more business travel, but this could be replaced by an increase in the use of video-conferencing. Ensuring that travel medicine is prepared to cope with whatever changes will occur is best brought about by encouraging the best possible collaboration between the tourism and aviation industries and the health professionals and promoters, so that the implications of the changes can be fully understood and used to better prepare the tourist for the risks, whatever they may be.

References

1. UNWTO (2009) Tourism Highlights 2009; http://www.unwto.org/facts/eng/highlights.htm (accessed 23 October 2009).

2. WTTC (2009) WTTC Results Show No Time for Rhetoric, press release 12 March; http://www.wttc.org/news-media/news-archive/2009/wttc-results-show-no-time-rhetoric/ (accessed 29 April 2012).
3. Page S (2009) Current issue in tourism: the evolution of travel medicine research: a new research agenda for tourism? *Tourism Management* **30**: 149–157.
4. Clift S and Grabowski P (eds) (1997) *Tourism and Health*. Pinter, London.
5. Steffen R *et al*. (2007) *Manual of Travel Medicine and Health*, 3rd edn. BC Decker, Hamilton.
6. World Health Organization (2009) International Travel and Health; http://www.who.int/ith/en/ (accessed 2 September 2009).
7. WTTC (2009) New Research Confirms that Mexico's Tourism will Remain Strong Over the Long Term, press release 10 August; http://www.wttc.org/news-media/news-archive/2009/new-research-confirms-mexicos-tourism-will-remain-strong-over-lo/ (accessed 29 April 2012).
8. Patterson I (2006) *Growing Older*. CABI, Wallingford.
9. Richards G and Wilson J (2006) Youth and adventure. In: Buhalis D and Costa C (eds) *Tourism Business Frontiers*, pp. 40–47. Elsevier, Oxford.
10. Marvel, M. (2006) Study tourism. *Travel and Tourism Analyst*, June.
11. Messerli H (2008) Adult gap years – international. *Travel and Tourism Analyst*, July.
12. Buckley R (2006) *Adventure Tourism*. CABI, Wallingford.
13. Dunford J (2008) Adventure tourism – Europe. *Travel and Tourism Analyst*, May.
14. Crouch G *et al*. (2009) Modelling consumer choice behavior in space tourism. *Tourism Management* **30**: 441–454.
15. McKelvie J (2005) Religious tourism. *Travel and Tourism Analyst*, March.
16. Mintel (2009) Health and wellness holidays – UK. *Mintel Leisure Report*, October.
17. Yeoman I (2008) *Tomorrow's Tourist*. Elsevier, Oxford.
18. Hunter-Jones P and Blackburn A (2007) Understanding the relationship between holiday-taking and self-assessed health: an exploratory study of senior tourism. *University of Liverpool Research paper*, 2007/31.
19. ACI (2009) *ACI Global Traffic Forecast Report 2008–2027*. ACI, Geneva.
20. Boeing (2009) Commercial Market Outlook 2009–2028. Boeing, Seattle.
21. Anno.aero (2009) US Propensity for Air Travel 15 Times Greater than in China; http://anna.aero/2009/10/23/us-propensity-for-air-travel-is-15-times-greater-than-in-China (accessed 23 October 2009).
22. Foreman E (2003) Just plane scared? An overview of fear of flying. In: Bor R (ed.) *Passenger Behavior*, pp. 45–59. Ashgate, Aldershot.
23. Zuckerman J (2003) Health and illness among airline passengers. In: Bor R (ed.) *Passenger Behavior*, pp. 232–235. Ashgate, Aldershot.
24. McIntosh I (2003) Flying-related stress. In: Bor R (ed.) *Passenger Behavior*, pp. 17–31. Ashgate, Aldershot.
25. The Moodie report (2007) *The airport retail study 2006–07*, The Moodie report, Brentford.
26. IATA (2009) Worldwide Scheduling Guidelines, 18th edn; http://www.euaca.org/FDownloadDocument.aspx?file=165 (accessed 23 October 2009).
27. Airbus (2009) Global Market Forecasts 2009–2028. Airbus, Toulouse.
28. Waterhouse J *et al*. (2003) Long-haul flights, travel fatigue and jet lag. In: Bor R (ed.) *Passenger Behavior*, pp. 246–260. Ashgate, Aldershot.
29. Dahlberg A (2003) Air rage post-9/11. In: Bor R (ed.) *Passenger Behavior*, pp. 95–117. Ashgate, Aldershot.
30. Grais F *et al*. (2003) Assessing the impact of airline travel on the geographic spread of pandemic influenza. *European Journal of Epidemiology* **18**: 1065–1072.
31. Tatem A *et al*. (2006) Global transport networks and infectious disease spread. *Advances in Parasitology* **62**: 293–343.
32. ICAO (2009) Guidelines for States Concerning the Management of Communicable Disease Posing a Serious Public Health Risk; http://legacy.icao.int/icao/en/med/AvInfluenza_guidelines.pdf (accessed 29 April 2012).

Chapter 3 Epidemiology of health risks and travel

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Global burden of infectious diseases

Significance of infectious diseases in developed countries

In industrialised countries, many infectious diseases were controlled successfully during the twentieth century through improvements in hygiene and sanitation, and the introduction of antibiotics and vaccines. As a consequence, infectious diseases were no longer viewed as important, and were regarded as almost having vanished in the developed world. However, during the past two decades there has been renewed interest in infectious diseases for various reasons, including an increase in the number of susceptible groups, such as the growing population of immunocompromised patients (e.g. organ transplant recipients, HIV-infected people or antiTNF-alpha recipients) who are at risk of opportunistic infections such as tuberculosis. New and old pathogens have been determined to either cause or contribute to cancers or other diseases considered in the past as non-infectious diseases (e.g. peptic ulcer disease). Changes in modern lifestyles have created new risks of acquiring certain infections. Last but not least, travel has contributed to the global spread of emerging and re-emerging infectious diseases (Table 3.1) as well as to the resistance to anti-infective drugs (Table 3.2).

Significance of infectious diseases in developing countries

Tropical infections

Tropical infectious diseases in a classical sense are limited geographically to areas where specific conditions of tropical climate and ecology must be present as a *conditio sine qua non* for the transmission and spread of the responsible pathogen. Typically, these diseases are transmitted by specific vectors (e.g. malaria, arbovirus infection, leishmaniasis, trypanosomiasis, filariasis), or require special intermediate hosts (e.g. schistomiasis and other helminthic infections), specific reservoirs (e.g. Lassa fever, monkeypox) or environmental conditions (e.g. stronglyoidiasis). Of all infectious diseases specific to the tropics, respiratory infections, diarrhoeal diseases and malaria are the main causes of death ([1], Table 3.3). Other tropical diseases, such as schistosomiasis and filariasis, are responsible for chronic morbidity in very large populations.

There are many other infectious diseases (e.g. cholera, leprosy, geohelminthic infections) that have been endemic worldwide but are now confined mainly or exclusively to developing countries in the tropics (Table 3.3). This is usually due to prevalent socioeconomic conditions and is largely independent of a tropical climate or other specific conditions associated with a tropical environment. Nevertheless, these infections are often regarded as typical tropical infectious diseases in a broader sense.

Infections in the tropics

In addition to specific and typical tropical infectious diseases, developing countries also carry the main burden of the most important infectious diseases occurring worldwide (Table 3.3). Infectious and parasitic diseases cause considerable morbidity and mortality in developing countries where they are still the leading cause of death (Table 3.3). Despite the continued increase in cancers, accidental injuries, obesity, diabetes and cardiovascular diseases, infections are the major reason for the enormous loss of life years as a result of disability and premature death [2], especially during childhood.

Last, developing countries are usually more affected by emerging and re-emerging diseases (Table 3.1), as appropriate methods of control are usually severely limited by a lack of resources and weak health system infrastructures. Often,

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Table 3.1 Important examples of emerging and re-emerging infectious diseases

Emerging	Re-emerging
HIV/AIDS	Tuberculosis
Lyme disease	Malaria
Haemolytic uraemic syndrome	Cholera
EHEC*	Dengue fever
Hantan pulmonary syndrome	Rift valley fever
Japanese encephalitis	African trypanosomiasis
Cyclosporiasis	Plague
Ebola haemorrhagic fever	West Nile fever
Lassa fever	Chikungunya
Ross River fever	Influenza H1N1
Nipah virus disease	
SARS-associated coronavirus	
Malaria (*Plasmodium knowlesi*)	

*EHEC = enterohaemorrhagic *Escherichia coli*.

Table 3.3 Global epidemiology of the most important infectious diseases (WHO estimates for 2002)

	No. of deaths (millions)	No. of cases (millions)	No. of infected persons (millions)
Respiratory infections	4.0	>1.0	–
Infectious diarrhoea	2.8	3.5	–
Tuberculosis	1.6	70–80	1.7
Malaria	1.3	300–500	–
HIV/AIDS	2.8	3.5	36
Total	11.5		
Global no. of deaths in 2002	57		
Deaths due to infections in 2002	15 (26%)		

From [1]

Table 3.2 Important examples of emerging resistance

Methicillin-resistant *Staphylococcus aureus* (MRSA)
Glycopeptide-resistant enterococci and staphylococci
Cephalosporines-resistant *Escherichia coli*
Penicillin-resistant *Streptococcus pneumoniae*
Fluoroquinolones-resistant *Neisseria gonorrhoeae*.
Fluoroquinolones-resistant Salmonella and other bacteria causing diarrhoeal disease
Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis
Chloroquine-resistant malaria (*Plasmodium falciparum, P.vivax*)
HIV

this also applies to the emergence of drug resistance, which has a significant impact on the treatment of serious pathogens (Table 3.2).

Dimensions of international travel and migration

During recent decades, global migration has expanded tremendously (Figure 3.1). Nowadays, the figures for worldwide travel have exceeded 900 million international arrivals, and it is estimated that there will be more than 1.6 billion travellers per annum by the year 2020 [3]. The leading travel destination continues to be Europe (460 million of travellers), followed by Asia, the Americas, the Middle East and Africa. Each year, about 50 million people travel from industrialised to developing countries. The reasons for international travel are mainly tourism, business and education; however, in some regions of the world, migrant workers and refugees contribute substantially to international migration (Table 3.4). In many developed countries, between 5% and 15% of the population were not born in the country in which they reside, with more than 75% originating from countries outside the developed world, including an increasing number of foreigners originating from tropical countries. The main reason for immigration to developed countries is poverty, whereas education and political reasons (refugees, asylum seekers) are less common.

Tropical infectious diseases and travel

Historically, the spread of tropical infectious diseases has been linked closely to migration. *Schistosoma mansoni* infection and onchocerciasis have been introduced to South and Central America most probably by the importation of Africans as slaves. Malaria has always targeted susceptible military troops and has decided the outcomes of many battles and wars. In addition, the spread of tropical infectious diseases is favoured typically by political crises and wars that are accompanied by significant movement of populations (e.g. refugees) and the concomitant breakdown of internal infrastructures within countries.

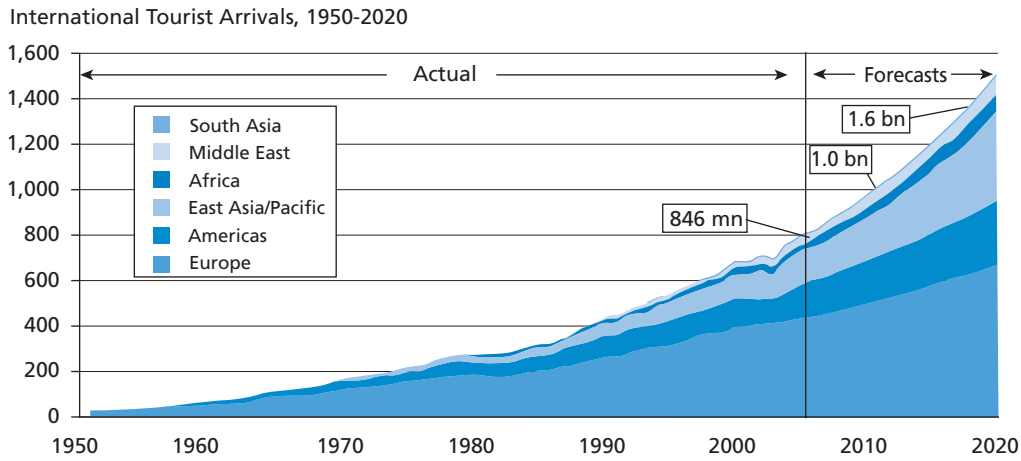

Figure 3.1 Travel statistics and forecast [4].

Table 3.4 International travel and migration (estimates)

Global world population (2005): 6.5 billion	
International travellers[a]	900 million[a]
Migrant workers including families[b]	190 million
Refugees[b]	13.5 million

[a]WTO (2008).
[b]UN-ESA (2006).

Table 3.5 Risk of importation and dissemination of some infections with epidemic potential in developed countries

Infection	Importation	Secondary cases	Epidemic spread
Ebola fever, Lassa fever	+	(+)	–
Yellow fever	+	–	–
Plague	+	(+)	–
Cholera	+ +	(+)	–
HIV infection	+ + +	+ + +	+ + +
Multidrug-resistant tuberculosis	+ +	+ +	+ +
Malaria	+ + +	–	–
Dengue fever	+ + +	–	–

Today, pathogens can travel at high speed, with travellers often acting as vectors, and are able to reach all parts of the world within 24 hours as demonstrated by the SARS epidemic; the same, however, rarely applies to tropical diseases. Highly contagious agents, such as influenza viruses, may cause epidemics in distant foci within a short time; however, most infections specific to the tropics need certain environmental conditions for autochthonous spread. Single cases may be exported worldwide, but further dissemination is limited to areas where suitable vectors, intermediate hosts, reservoirs or ecological conditions are present (Table 3.5). Nevertheless, some infections originating in tropical countries have shown potential for global spread. Human immunodeficiency virus (HIV) is a formidable example of such a pathogen. Occasionally, even tropical 'high-risk' pathogens (e.g. Lassa virus, Ebola virus, Marburg virus) may be exported to non-endemic areas (Table 3.6). However, the risk of further spread as a consequence of migration seems to be low at the moment because the known or presumed zoonotic reservoirs are probably restricted geographically, and human-to-human transmission seems to be limited to close contacts and to nosocomial spread under poor hygienic conditions (Table 3.5). Nevertheless, the future emergence of new pathogens combining high pathogenicity and high infectivity and/or resistance against available drugs cannot be excluded.

Sometimes the conditions for successful spread of a tropical pathogen are exported well in advance of the pathogen establishing itself. For example, reinfestation with *Aedes aegypti* in South America and the export of the Asian 'tiger mosquito' *A. albopictus* by scrap vehicle tyres to the US and southern Europe have provided the environment for the autochthonous spread of dengue and chikungunya viruses [4]. In addition, global warming and short-term climatic fluctuations (e.g. El Niño) may facilitate the spread of vectors and pathogens of tropical infectious diseases (e.g. malaria, dengue fever) to more temperate climates [5].

Table 3.6 Imported cases of viral haemorrhagic fever that may be transmitted directly from human to human in developed countries, since 1989

Year	Virus	Imported to
1989	Ebola-Reston	US
1992	Ebola-Reston	Italy
1994	Ebola-Ivory Coast	Switzerland
1995	Ebola-Zaire	Italy
1996	Ebola-Reston	US
1996	Ebola-Zaire	South Africa
2000	Lassa (3)	Germany, Netherlands, UK
2003	Lassa	UK
2004	Lassa (2)	UK, US
2005	Crimean-Congo	France
2006	Lassa	Germany
2008	Marburg	Netherlands
2008	Lassa	UK
2009	Lassa	UK

Migration also contributes to the biological interplay between pathogens and their hosts, as well as between different infective agents. Genetic exchange between different strains or species (e.g. influenza viruses, HIV, enterobacteria, schistosomes) within the same host or between human and zoonotic reservoirs may result in the emergence of pathogens with altered virulence, immunogenicity or sensitivity to drugs.

More than ever before, migration is the major driving force for the dissemination of new and old infectious diseases and associated problems (e.g. drug resistance). As an important consequence of these effects of globalisation, the health problems of tropical countries are gaining more worldwide significance and attention today.

Health risks to travellers

It is thought that approximately 50% (20 to 70% according to various studies) of travellers abroad complain of travel-related illness, whereas approximately 10% consult a physician on their return [6]. The epidemiology of travel-associated illness may be evaluated through different means and in different settings [7]. Generally, two different categories of data are available. The majority of published studies, particularly those disseminated by the disease surveillance networks (e.g. GeoSentinel, TropNetEurop), focus on the epidemiology of travel-associated illness that occurs after travel (*see* Chapter 15), whereas other studies determine the epidemiology of diseases occurring during travel. The spectrum of travel-related diseases and their frequency may, however, vary substantially. For instance, in a cohort of American travellers, 64% complained of illness during travel, whereas 26% became ill on their return; on the other hand, 8% of the travellers who were unwell during their trip consulted a physician abroad, whereas 12% of those who were unwell after travel sought advice on their return [8]. Another important source of bias is that the different purposes for travel (tourism, business, residence, immigration, etc.) and the country/place visited are rarely taken into account. Even the apparently uniform group represented by 'tourists' actually comprises backpackers, trekkers, subaqua divers, organised groups and so on. These studies have formed the basis of a proposed incidence scale of more important diseases and conditions to which travellers may be exposed as a consequence of travelling (Figure 3.2) [9].

Cohort studies

The most informing data have been obtained from epidemiological studies based on questionnaires completed during pre-travel consultations or while flying. These provide a general approach to the problem, regardless of the destination, and enable the calculation of disease attack rate by dividing the number of ill travellers (numerator) by that of all the people that travelled during the same time (denominator). Nonetheless, the true denominator to assess travel-associated health risks would include a representative cohort of travellers who are assessed prospectively in terms of health problems, GP consultations and other medical resources, including hospitalisation, during and after travel. Some large studies have been based on questionnaires in which travellers describe health problems arising during the trip [8, 10–13]. The response rate to such questionnaires was about 75%.

The proportion of travellers who fall ill varies from 15 to 64%: 15% of 7,886 Swiss travellers [13]; 21% of 26,119 American travellers [10]; 33% of 2,665 Finnish travellers [12]; 43% of 2,211 British travellers [11]; and 64% of 787 American travellers [8]. Among the Swiss travellers, 1.6% consulted a specialist in tropical medicine on their return, while 4.2% saw a primary care doctor [13]; 5.4 to 26% of American travellers saw a doctor on their return [8, 10]. Five per thousand travellers were admitted to hospital [13].

Overall, these studies show that the leading health problems during travel are: diarrhoea, accounting for half to two-thirds of health problems; upper respiratory tract infections (14–31%); skin diseases (10–20%); and fever (12–15%). Sexually transmitted infections are also a frequent cause of morbidity. Genital discharge and ulcerations were reported by 0.6% and 0.1%, respectively, of 7,886 Swiss travellers [13]. In a cohort of 2,665 Finnish travellers, 39% of

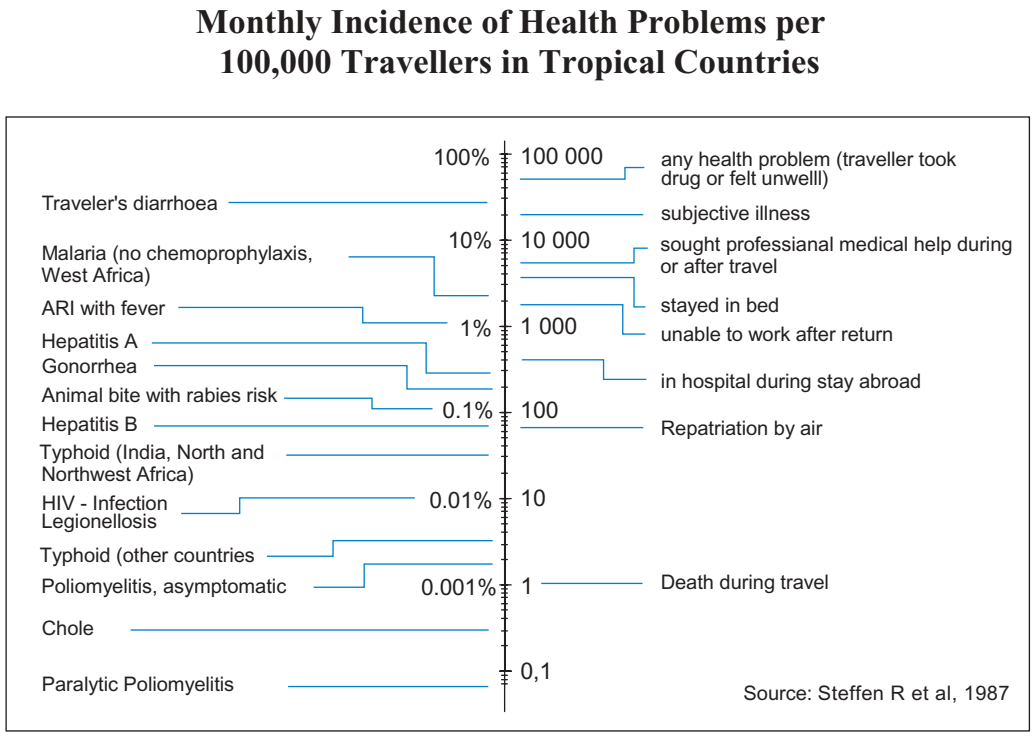

Figure 3.2 Health problems during a stay in developing countries: incidence rate per month [9].

round-the-world travellers and 30% of tourists to Thailand reported participating in 'at-risk' sexual behaviour [12].

These studies demonstrate significant differences in their findings regarding the traveller, their destination and type of travel. Overall, travel health problems are significantly more frequent among young adults, travellers to West Africa, backpackers, those travelling for long periods, people working abroad and travellers staying with local residents.

Field studies

Studies carried out in the field by local doctors provide useful information on travel-associated diseases. Three such studies have been conducted in Nepal. Among the 12,437 French tourists who stayed in Nepal in 1984, 838 (6.7%) consulted the doctor at the French Embassy; they had a total of 860 health problems, including diarrhoea (29.6%), ear, nose and throat (ENT) infections (17.7%), skin conditions (12.4%), fever (8%) and sexually transmitted diseases (4%). Ten travellers (0.08%) were admitted to hospital, nine (0.07%) were evacuated, 15 (0.12%) were repatriated, two underwent surgery locally and one died [14]. A similarly designed study was completed 17 years later and showed comparable results with a rising incidence of consultations for altitude sickness (travellers evacuated from the Himalayas) and upper respiratory infections, whereas sexually transmitted infections were less prevalent [14]. The third study carried out in Kathmandu involved 19,616 travellers, representing all nationalities, presenting to a private clinic [15]. The main illnesses were gastrointestinal infections (31%), respiratory tract infections (21%) and skin conditions (10%); the frequency of diarrhoea (shigellosis and giardiasis) was higher during the hot season preceding the monsoon.

Travellers to the Maldives and Fiji appear to experience a different pattern of travel-related illnesses. In the Maldives, ear infections (often otitis externa), superficial injuries (often due to coral and shellfish) and solar allergies represented 24%, 14% and 13%, respectively, of presenting illnesses [16]. In Fiji, ear problems, injuries (some resulting from exposure to the marine environment) and skin rashes (often related to sun exposure) each accounted for 10% of visits to a doctor, while skin infections accounted for 13% and gastrointestinal disorders for 20% [17]. In both these studies carried out in islands particularly popular with tourists, diarrhoea, upper airway infections (excluding otitis externa) and fever were less frequent presenting illnesses than in Nepal.

It is clear that travel diseases vary according to the country visited: diarrhoea and upper airway infections are prevalent in colder, mountainous regions such as Nepal, while skin

Table 3.7 Spectrum of disease and relation to place of exposure among ill returned travellers [18]

Most common diagnoses (total population 17,353)	All regions	Subsaharan Africa	Southeast Asia	South America
Diarrhoea	**33%**	23%	31%	35%
– acute	22%	17%	21%	22%
– persistent (>14d)	11%	6%	10%	13%
Systemic febrile illness	**23%**	37%	25%	14%
Dermatologic disorder	**17%**	13%	21%	26%
Non-diarrhoeal GI disorder	8	7%	6%	8%
Respiratory disorder	8%	8%	10%	5%
Genitourinary inc. STD	4%	5%	3%	3%
Underlying chronic diseases	2%	2%	1%	2%
Injury	1%	1%	1%	1%

conditions and superficial injuries are more common in coastal areas.

Post-travel illnesses

An increasing number of studies recently published provide information on the spectrum of diseases seen in returning travellers. In the largest international study published by GeoSentinel, the Global Surveillance network of ISTM and CDC, where 17,353 returning sick travellers (median age: 33; sex ratio: 1) were included, the main causes of consultation (in travel disease units or hospitals) were acute diarrhoea (22.2%), skin diseases (17%), chronic diarrhoea (11.3%), fever of unknown origin (9.1%) and respiratory infections (7.7%) ([18], Table 3.7).

Nonetheless, all these studies took place in units specialised in travel medicine or in infectious and tropical diseases, and such an evaluation may be a source of referral or selection bias. According to one study performed in the community involving general practitioners [19], the main causes of ill health were gastrointestinal problems (35%), respiratory tract infections (30%) and skin diseases (11%). Of note, systemic febrile illness and imported tropical disease accounted for less than 4% of cases each. Malaria was very uncommon (3%) when compared with studies performed in academic or tertiary care units where this figures varied from 8% to 26% [18, 20–24].

These different results suggest that the studies performed in specialist infectious/tropical disease and travel medicine units probably overestimate the impact imported infectious diseases have within the spectrum of travel-associated diseases. On the other hand, these studies underestimate the impact from non-infectious diseases. Otherwise, studies of returning sick travellers have generally focused on different signs and symptoms (fever, diarrhoea, skin diseases, pneumonia) or specific diseases. The most common of these health hazards have been determined to be malaria (*see* Chapter 10), dengue (*see* Chapter 7), tuberculosis infection (*see* Chapter 8), hepatitis A (*see* Chapter 7), enteric fever (*see* Chapter 8) and hepatitis B (*see* Chapter 7). Sexually transmitted infections are another cause of illness in returning travellers [25].

Travel-associated mortality

The incidence of death has been estimated at 1 per 100,000 travellers per month [9]. In 1989, Hargarten assessed the causes of death abroad in 2,463 American tourists in 1975 and 1984 [26]. The main causes were cardiovascular conditions (49%), road accidents (7%), drowning (4%) and other accidents (12%); in 25% of cases the cause of death was unidentified, while infectious diseases accounted for only 1% of fatalities (Table 3.8). Two further studies have been conducted in the US and Canada, which confirmed the major role road accidents, drowning and cardiovascular disease have, whereas the cause of death was unidentified in about 25% of the cases and infections were rarely the cause of death.

The frequency and severity of road accidents in tropical countries explains why they are also the most common cause for medical evacuation. With regard to traffic accidents, those involving motorcycles are especially common among tourists. In Bermuda, one study showed that motorcycle accidents accounted for 92% of all traffic injuries among tourists, compared with 71% among residents. The rates of motorcycle-related injuries were respectively 94 per 1,000 person-years among tourists and 16 per 1,000 person-years among residents (relative risk for tourists: 5.6). The highest

Table 3.8 Causes of death among tourists (different studies)

Cause of death	Hargarten *et al.* 1991 (n = 2463)	Steffen *et al.* 2003 (n = 247)	Steffen *et al.* 2003 (n = 68)	Provic *et al.* 1995 (n = 421)	Paixao *et al.* 1995 (n = 952)	McPherson *et al.* 2007 (n = 2410)
Origin destinations	US anywhere	Swiss Europe	Swiss overseas	Australia overseas	Scotland anywhere	Canada anywhere
Cardiovascular	**49%**	**14%**	**15%**	**35%**	**69%**	**52%**
Infection	1%	nd	3%	2%	4%	nd
Cancer	6%	nd	nd	nd	nd	nd
Injury/accident	**36%**	**23%**	**44%**	**54%**	**21%**	**19%**
– traffic	7%	13%	12%	28%	nd	nd
– air crash	2%	4%	12%	nd	nd	nd
– drowning	4%	4%	9%	nd	nd	nd
– other	23%	2%	11%	26%	nd	nd
Suicide/homicide	3%	nd	nd	8%	nd	8%
Other, unknown	19%	58%	29%	17%	7%	nd

rate among tourists was found in the 50–59 year age group. The significantly higher rate of motorcycle accidents among tourists may be related to the use of unfamiliar vehicles in unknown surroundings, inexperience and the requirement to drive on an unfamiliar side of the road in Bermuda [27]. With regard to returning worldwide travellers, mortality related to malaria, pulmonary embolism, pneumonia and pyogenic abcess was estimated to be 1 per 1,000 unwell travellers in a GeoSentinel study [18].

The epidemiology of health risks associated with travel should be considered and updated regularly. Travellers comprise an important group from whom sentinel surveillance and epidemiological data may be collated because the diseases acquired during travel are representative of the diseases prevalent in the country visited. Moreover, some of the diseases imported by travellers may spread in the community and become of public health importance. Travellers also provide unique opportunities to better understand the natural history of tropical infections, their clinical presentations and the effectiveness of the necessary treatments.

References

1. WHO (2004) *The World Health Report 2004*. World Health Organization, Geneva, Switzerland.
2. WHO (2009) *World Health Statistics 2009*. World Health Organization, Geneva, Switzerland.
3. United Nations Department of Economics and Social Affairs, Population Division (2006) Tourism 2020 Vision. New York, USA.
4. WTO (2008) *Yearbook of Tourism Statistics 2007*. World Tourism Organization, Madrid, Spain.
5. Maskell K *et al.* (1993) Health and climate change: basic science of climate change. *Lancet* **324**: 1027–1031.
6. Ryan ET *et al.* (2002) Illness after international travel. *N Engl J Med* **347**: 505–516.
7. Leder K *et al.* (2008) Comparative analysis of methodological approaches used for estimating risk in travel medicine. *J Travel Med* **15**: 263–272.
8. Hill DR (2000) Health problems in a large cohort of Americans travelling to developing countries. *J Travel Med* **7**: 259–266.
9. Steffen R *et al.* (2008) Health risks among travellers – need for regular updates. *J Travel Med* **15**: 145–146.
10. Kendrick MA (1972) Study of illness among Americans returning from international travel. *J Inf Dis* **126**: 684–685.
11. Reid D *et al.* (1980) Infection and travel: the experience of package tourists and other travellers. *J Infect* **2**: 365–370.
12. Peltola H *et al.* (1983) Trips to the south-a health hazard. Morbidity of Finnish travelers. *Scand J Inf Dis* **15**: 375–381.
13. Steffen R *et al.* (1987) Health problems after travel to developing countries. *J Inf Dis* **156**: 84–91.
14. Hochedez P *et al.* (2004) Changes in the pattern of health disorders diagnosed among two cohorts of French travellers to Nepal, 17 years apart. *J Travel Med* **11**: 1–6.
15. Shlim DR (1992) Learning from experience: travel medicine in Kathmandu. In: Lobel HO *et al.* (eds) *Travel Medicine 2, Proceedings of the 2nd Conference on International Travel Medicin*, pp 40–42. ISTM, Atlanta, 1991.
16. Plentz K (1992) Nontropical and noninfectious diseases among travelers in a tropical area during a five-year period (1986–1990). In: Lobel HO *et al.* (eds) *Travel Medicine 2, Proceedings of the 2nd Conference on International Travel Medicin*, p. 77. ISTM, Atlanta, 1991.
17. Raju R *et al.* (1991) Incidence of minor and major disorders among visitors to Fiji. In: Lobel HO *et al.* (eds) *Travel Medicine 2, Proceedings of the 2nd Conference on International Travel Medicine*, p. 62. ISTM, Atlanta, 1991.

18. Freedman DO *et al*. (2006) Spectrum of disease and relation to place of exposure among ill returned travellers. *N Engl J Med* **354**: 119–130.
19. Caumes E *et al*. (2008) Health problems in returning travelers consulting general practitioners. *J Travel Med* **15**: 457–459.
20. O'Brien DP *et al*. (2006) Illness in returned travelers and immigrants/refugees: the 6-year experience of two Australian infectious diseases units. *J Travel Med* **13**: 145–152.
21. Nothdurft HD and Löscher T (1993) Imported infections in German travelers returning from tropical countries. Program and Abstracts of the 3rd Conference on International Travel Medicine, Paris, p. 86 (abstract 39).
22. Fenner L *et al*. (2007) Imported infectious diseases and purpose of travel, Switzerland. *Emerg Inf Dis* **13**: 217–222.
23. Stienlauf S *et al*. (2005) Epidemiology of travel-related hospitalization. *J Travel Med* **12**: 136–141.
24. Ansart S *et al*. (2005) Illnesses in travelers returning from the tropics: a prospective study of 622 patients. *J Travel Med* **12**: 312–318.
25. Ansart S *et al*. (2009) Sexually transmitted diseases diagnosed among travellers returning from the tropics. *J Travel Med* **16**: 79–83.
26. Hargarten SW *et al*. (1991) Overseas fatalities of United States citizen travelers: an analysis of deaths related to international travel. *Ann Emerg Med* **20**: 622–626.
27. Carey MJ and Aitken ME (1996) Motorbike injuries in Bermudas: a risk for tourists. *Ann Emerg Med* **28**: 424–429.

Chapter 4 Fitness to travel

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Introduction

When Sylvain Bédard became the first heart transplantation recipient to climb above 6,000 metres in 2000, his achievement was highly publicised. Numerous foundations and organisations looking for prestigious and highly publicised activities are also taking celebrities and prominent business people to Kilimanjaro and other high summits to raise funds. The typical traveller reading such stories can easily forget that these are exceptional exploits not without risk to most average individuals. It is also easy to forget that Sylvain Bédard's exploits were made possible because of the strict medical supervision he was under and because he had completed months of intensive training.

In 2009 in Canada, the humble tale of a television star announcer was the awakening call for travellers and many healthcare professionals about the risky business of travelling to high altitude. It all started with the dream of a cardiologist, Dr Michel White, of the Montreal Heart Institute, who wanted to convince baby boomers that it was never too late to regain control of their cardiovascular health. He chose the most eloquent vehicle: television. The preparation and the trip were recorded for a science show called *Découverte* for the Canadian national broadcasting network, CBC.

Led by Michel White and Heather Ross, medical directors of the cardiac transplant programme at University Health Network, and accompanied by other experts and a television crew, Charles Tisseyre, a science show series narrator, was just another climber in a group of baby boomers ranging from 44 to 64 years old, including two who were recipients of a heart or kidney transplant. They were all committed to a rigorous workout schedule, they consulted a travel clinic for immunisations and prescriptions well in advance of their trip, carried the perfect equipment in a light backpack and had access to a nutritionist who prepared their well-balanced meals. Strict medical supervision was available constantly as they all travelled together. And, well… Charles Tisseyre failed and had to stop on day seven, watching the others succeed and reach the 6,476-metre summit of Mount Mera in Nepal. He generously agreed to continue to be part of the documentary. He wanted to portray their resilience against the challenges involved in such a climb, and also draw attention to the importance and risks associated with travel to high altitude, including sleep apnoea and loss of weight among others.

Very few travellers will seek the advice of a travel medicine specialist to understand if they are 'fit to travel'. Most have already taken the decision to travel before attending a travel health consultation, even in the presence of very serious health conditions. It may be, of course, because they lack knowledge about the associated travel health risks. The potential travel health risks associated with travel to different environments and climates are not known by the typical traveller and the impact of their own medical condition is also often dismissed. The traveller may feel that the trip cannot be postponed or the itinerary cannot be changed for any number of reasons: a wedding to attend; a relative who may be dying; a chronic disease putting the traveller's own life at risk; a special religious gathering; or the desire to visit a magnificent site that someone wants to see before dying. Whatever the reason, many will travel to places a travel medicine practitioner would prefer them not to go to. A simplistic approach would be to deny the traveller 'a licence to travel'. It seems more reasonable, however, to try to inform the traveller of the potential travel health risks, as a travel health practitioner to know how to evaluate their 'fitness to travel', and what recommendations to give to help them avoid some of the risks and diminish the impact of the ones that are inevitable. The travel healthcare practitioner must keep in mind that the purpose of the consultation is not to discourage travelling but rather to provide travellers with the best

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counselling possible in accordance with their health status and the type of travel planned.

Fitness to travel is thus a complex issue to evaluate. Although most would not want to unduly prevent a 'last wish' in an individual's life to be fulfilled, most would prefer to see their travellers return home safely after their journey. Maintaining the good health of travellers is the major purpose of travel medicine. It is important to individualise counselling regarding the possibility of contracting travel health-related illnesses, for example malaria; giving advice about the prevention of sexually transmitted infections, including HIV, avoiding gastrointestinal illness and even how to prevent transmission of the common cold. A travel health consultation includes assessing the individual's health and if they have a history of allergies, the need for a Medic-Alert product and adrenaline (epinephrine) to be carried along with a first-aid kit.

All travel health consultations should begin with gathering the basic information concerning the planned trip. To advise travellers correctly, it is important to ask about all the countries and regions to be visited, with questions regarding possible stay, particularly at night, in rural areas. It is also important to know the exact period and duration of the travel, with special attention given to the season, which may influence the risk of contracting malaria and other infectious diseases. Travellers returning to their native country to visit family will often venture to more remote areas and take fewer precautions concerning malaria and food hygiene. All planned or possible activities must be identified and for those without a plan, an effort should be made to highlight areas that require special travel health considerations.

The traveller's personal health and impact on fitness to travel

The gathering of information begins as soon as you ask the traveller into your office. The pace of walking, the use of assistance such as a cane, high body mass index, hearing or vision impairments are all essential information. An elderly traveller may benefit from a suggestion to receive herpes zoster vaccine as fatigue is an important risk factor associated with infection. A significant number of older travellers are not appropriately immunised against pneumococcal infection and influenza, and the travel health consultation provides an opportunity to address these.

The purpose of this chapter is to highlight specific issues that could increase the risk of morbidity and mortality to travellers. For more detailed information, the reader is referred to the specific chapters.

All travellers with a pre-existing medical condition should be advised to carry a copy of their medical records, which should include an assessment of their medical condition, a full list of their medications with dosage and generic names; for pregnant women date of expected delivery; a recent copy of an electrocardiogram; a list of allergies; a copy of recent laboratory results and imaging, which can be stored on an electronic device with the appropriate program to open the data. Table 4.1 summarises special considerations for travellers.

Table 4.1 Special considerations for some travellers

Individuals	To be considered
Allergic traveller	Medic-Alert products and adrenaline (epinephrine); carry a picture of food allergens
Customer of size	Rules regarding extra seat; antifungal treatment; foot care
Elderly traveller	Vaccines against pneumococcal infection, influenza and herpes zoster
Diabetic traveller	Medic-Alert products; letter of authorisation for syringes; fast-acting sugars and snacks; foot care; vaccines against hepatitis B, pneumococcal infection, influenza, ETEC/cholera and herpes zoster; antifungal treatment
Cardiorespiratory problems	Oxygen during flights; special transport at airport
Pregnant traveller	Fetal ultrasound; compression stockings; oxygen supplement; placental cord clamp
Epileptic traveller	Medic-Alert products; careful choice of malaria prophylaxis
Immunocompromised traveller	See specific tables
Anxious travellers	Identify a local contact; hypnotics

'Traveller of size'

An increasing number of airlines, such as American Southwest, have a detailed set of rules regarding passengers needing spill-over space, who must purchase a second seat; if the flight ends up having extra space, the cost of that ticket may be refunded. The usual rule reads as follows: 'Customers who are unable to lower the armrests (the definitive boundary between seats) and/or who compromise any portion of adjacent seating should proactively book the number of seats needed.'

In extreme heat and humid conditions, such travellers are more prone to various forms of tinea. Recommendations regarding hygiene are important and their first-aid kit should include a treatment for the condition. Foot care also deserves special attention and should be discussed.

Diabetes

The initial evaluation of a diabetic traveller should include the individual's understanding of his or her own disease and what to do in case of complications while abroad. This includes:

- the availability of healthcare in the areas visited
- the understanding of hypo/hyperglycaemia (usually capillary blood) and the availability of laboratory blood testing
- the possibility of carrying insulin for the whole trip or the need to make adjustments using drug preparations manufactured locally (insulin preparations vary quite significantly from one country to another)
- the understanding of the importance of foot care
- the role of the sun and its effect on a more rapid absorption of insulin
- the adjustment of the dose of insulin needed for jet lag
- the need to carry syringes, needles, etc., to be accompanied by a letter of authorisation provided by a medical practitioner.

Diabetic patients should be prepared for travel like most other travellers. They can be given all the vaccines indicated and there are no specific contraindications to administration of any of the travel vaccines or drugs, e.g. malaria prophylaxis. Special attention should be taken to ensure that influenza and pneumococcal immunisations are up to date. Hepatitis B vaccination is strongly recommended as diabetics are at greatest risk of receiving healthcare and injections abroad. As diarrhoea might significantly alter glycaemic balance, the ETEC/cholera vaccine may be considered. Prophylactic antimicrobial agents are not generally recommended for diabetic travellers. The use of fluoroquinolones such as ciprofloxacin is considered the drug of first choice for the treatment of travellers' diarrhoea. As an alternative for the self-treatment of travellers' diarrhoea, co-trimoxazole, azithromycin or clarithromycin might be dispensed. Bismuth subsalicylate (Pepto-Bismol) should be used with caution.

For those over 50, the vaccine against herpes zoster would also be highly recommended. The first-aid kit should include broad spectrum antibiotics with instructions on how and when to use them. In extreme heat and humid conditions, these travellers are more prone to various forms of infection with tinea. Recommendations regarding hygiene are important and their first-aid kit should include a treatment for the condition. Foot hygiene is extremely important for any diabetic patient. Special care needs to be taken to avoid injuries during periods of travel. Blister dressings are useful for decreasing friction on a foot sore and decreasing the risk of ulceration. Sensible and comfortable shoes are essential if walking is planned.

Diabetic patients should be ultra-cautious when travelling and always be prepared for long delays. This means carrying extra food, medications and glucagon in carry-on bags and not in check-in luggage that will not be accessible during the journey. They should be aware that special meals can easily be ordered on most flights or cruises if requested, ideally one week in advance of travel. Insulin is stable at room temperature for about one week, but extremely hot temperatures should be avoided. Insulin can thus be transported easily in carry-on bags. Insulin should not be placed in luggage carried in the hold of an aeroplane as it may freeze during long flights. Travellers with diabetes should carry their own needles and syringes, even if they are not taking insulin. All travellers carrying needles and syringes should be provided with a letter on official stationery signed by the attending physician. An example of such letter is shown in Figure 4.1. A Medic-Alert bracelet (engraved with the wearer's allergies or other medical conditions) is also recommended. Malaria prophylaxis should be used when recommended.

Diabetic patients should take all necessary precautions to avoid hypoglycaemia. Fast-acting sugars and snacks should be carried, as well as glucagon. When travelling alone, a person in charge (a flight attendant, tour guide) should be informed of the treatment to be given in case of suspected hypoglycaemia. To decrease the risks, doses of insulin may be omitted on long trips when several time zones are being crossed. With severe jet lag, hyperglycaemia is preferable to hypoglycaemia. Diabetic travellers should be advised to never overlap two insulin injections. Information on countries to be visited and services for diabetic patients can be obtained from the International Diabetes Federation, who can also provide a card with blood glucose equivalents for different countries (*see* Additional resources at the end of this chapter).

Cardiorespiratory problems

Cardiopulmonary conditions that are not well controlled can result in major problems, especially during flights or when staying in places at high altitude. Very few studies have evaluated the safety of air travel following myocardial infarction (MI). In addition to concern over the risks of ischaemia during the flight, a number of travellers have experienced a myocardial infarction while abroad or close to the time of planned travel.

CERTIFICAT MÉDICAL – MEDICAL CERTIFICATE – CERTIFICADO MÉDICO

En faveur de :

(In favor of : – *A favor de : Em favor de :)*

Date:

(Date: *Fecha: Data*:)

Object : medication, medical kit, syringes and needles
Objet: Médicaments, trousse médicale, seringues et aiguilles
Objeto: medicamentos, botiquin, medico, jeringas y aguyas
Objeto: medicamentos, kit de primeiros socorros, seringas e agulhas

We, fully accredited doctors, attest that the person mentioned above is carrying with her/him, medication, a medical kit, sterilized syringes and needles for personal use during their trip. All these objects are not for retail sale and were prescribed by personal medical use.

Nous, médecins dûment autorisés, attestons que la personne ci-dessus mentionnée, transporte avec elle des médicaments, une trousse médicale, des seringues et des aiguilles stériles pour son usage personnel au cours du voyage. Tous ces objets ne sont pas destinés à la vente et ont fait l'objet d'une ordonnance médicale personnelle.

Nosostros, medicos debidamente autorizados, certificamos que la persona arriba mencionada transporta medicamentos, un botiquin medico, jeringas y agujas estériles para su uso personal durante et viaje. Todos esos objetos no son destinados a la venta y son parte de una prescripcion médica personal.

Nós, médicos devidamente autorizados, certificamos que a pessoa acima mentionada transporta medicamentos, kit de primeiros socorros, seringas e agulhas estéreis pa i seu uso pessoas durante a viagem. Todos esses objetos não são destinados à venda são parte de sua prescrição médica.

The Medical Director.

Figure 4.1 Example of a letter of authorisation.

High altitude increases the work of the heart during the first days of acclimatisation and travellers who have symptomatic heart disease may experience cardiac symptoms and a deterioration of their health when travelling at high altitude.

According to the Aerospace Medical Association (ASMA), a person who cannot walk at a fast pace or go up one single flight of stairs without shortness of breath at sea level is likely to be unwell at high altitude, including while travelling by air. Oxygen can be provided during the journey on most commercial flights, without problem. Arrangements for oxygen to be available on a flight need to be made by an experienced physician at least one week in advance of departure. A nasal canula, when available, to administer oxygen is often more comfortable than a mask. Travellers with congestive heart failure should not travel above 8,000 feet (2,400m). A delay of two or three weeks should be observed following MI or after a percutaneous coronary intervention (stent).

Asthmatic travellers should be prepared for sudden exacerbation of their symptoms while travelling by air. The dryness of the air aboard a plane, an unexpected exposure to or a change in the concentration of an allergen, an increase in the level of activities while travelling and respiratory

borne infections are all possible triggers of an asthmatic attack. Asthmatic travellers and those with chronic obstructive pulmonary disease (COPD) may also benefit from supplementary oxygen while flying. Pre-flight testing including a 'fitness to fly' test is available for such travellers in some tertiary respiratory centres.

Any traveller can request that special transport be made available in most airports. Reservation is not essential but is to be recommended if the transit time between flights is tight.

Food allergies

Allergies and anaphylaxis are potentially severe, life-threatening problems for the traveller. Allergies to egg protein and antibiotics are contraindications to some vaccines, such as yellow fever. Severe food allergy in a country where travellers may have difficulty in communicating and making themselves understood, is a life-threatening condition. Carrying pictures of the ingredients or food to be avoided could help, but will not guarantee the safety of meals consumed. In such circumstances, it is advisable to carry adrenaline (epinephrine) and a Medic-Alert bracelet or card. When travelling alone, a person in charge (a flight attendant, tour guide) should be informed of the treatment to be given in case of suspected anaphylaxis.

Pregnancy

Pregnancy needs more than passing attention. Pregnancy is not per se a contraindication to any travel, except for travel by air, as commercial airlines may limit travel near the expected time of delivery. Certain precautions need to be taken to protect the developing fetus and the mother in specific situations.

Before any trip far from home, overseas or involving difficult living conditions without ready access to healthcare, a pregnant woman should undergo a careful medical assessment. An ultrasound should be carried out to eliminate an extra-uterine pregnancy or a placenta praevia. The pregnant traveller and her companion should be informed of signs of possible labour or complications, and of the basic emergency procedures to be performed if needed. A placental cord clamp can be carried.

Pregnancy increases the risk of thrombophlebitis, as does a long trip at high altitude. A pregnant woman with varicose veins or an increased risk of deep vein thrombosis (DVT) should follow the following recommendations carefully:

- drink a lot of water
- request an aisle seat to enable leg stretching
- walk a few steps every hour
- do not cross your legs
- do not use sleeping pills or a muscle relaxant which might increase blood stasis.

In the presence of severe anaemia (haemoglobin less than 8.5 g%), oxygen should be provided during air travel. Arrangements for oxygen to be available need to be made by an experienced physician at least one week in advance. Wearing compression stockings to decrease the risk of DVT and increase comfort should be encouraged.

Live vaccines are to be avoided whenever possible for pregnant women, especially during the first trimester. Most obstetricians would advise vaccination to be given after the first trimester. In most situations, however, the risk of a serious infection far outweighs the minimal known risk or the theoretical risk of vaccination. A careful risk–benefit assessment should be made in each case. Please refer to Chapter 25 for further details.

Malaria is a common and serious infectious disease transmitted from dusk to dawn by mosquito bites. Personal protective measures are very effective in reducing the risk of contracting malaria. All pregnant travellers to endemic areas should be counselled about the use of insect repellent containing 35% or less of DEET on their exposed skin and the use of bed nets, and advised to wear clothing that reduces the area of exposed skin. Insecticides such as permethrin or deltamethrin on clothes and bed nets are very safe and can reduce the risk further.

In many endemic areas, malaria prophylaxis should be taken to reduce the risk significantly (but never completely). Some drugs are contraindicated during certain stages of pregnancy, but in most cases an acceptable alternative is available. This is especially important when a woman will inevitably be exposed to malaria.

Prophylactic antimicrobial agents are not generally recommended for pregnant travellers. The use of fluoroquinolones such as ciprofloxacin is relatively contraindicated. As an alternative for the self-treatment of travellers' diarrhoea, co-trimoxazole, azithromycin or clarithromycin may be offered. Bismuth subsalicylate (Pepto-Bismol) should be avoided. Administration of the inactivated ETEC/cholera vaccine to pregnant women may be considered after careful evaluation of the benefits and risks.

Travel insurance can and should be obtained before departure. After the 24th week of pregnancy, this insurance should include coverage for the newborn baby, in case of premature labour.

The elderly traveller

There is no age limit for travel. Health conditions, including cognitive fitness, are the only aspects that should be

evaluated. All aged travellers should remember that they may be more susceptible to illness during long trips and that such trips may be more strenuous. Luggage should be sensible, including luggage on wheels and using porters when available. Updating all immunisations is important and special attention should be given to tetanus, pneumococcal infection and influenza. As fatigue can be a trigger for shingles, the herpes zoster vaccine should be offered. As such travellers might be at higher risk of requiring medical and dental care while travelling, hepatitis B vaccine should be recommended.

The epileptic traveller

Epileptic patients going to malaria endemic areas should receive counselling from an experienced travel health practitioner. Most malaria prophylaxis preparations are either contraindicated or are associated with an interaction with their usual prescriptions. Chloroquine and mefloquine are generally contraindicated. Nevertheless, malaria chemoprophylaxis is usually possible. Epileptic travellers should be recommended to wear a Medic-Alert bracelet or card. When travelling alone, a person in charge (a flight attendant, tour guide) should be informed of the treatment to be given in case of a suspected epileptic convulsion.

Travellers with psychiatric conditions

Travelling to exotic destinations can certainly be a rewarding activity. However, the long journey, the jet lag and change in sleeping habits, the confrontation with new cultures and living conditions, the lack of references and the language barriers can result in anxiety and travel fatigue. Travel should thus be regarded as a stressful event that will rarely help unstable individuals. Long-distance and long-term travellers are at higher risk of emotional distress, especially if they travel alone in areas far from home. The negative effect of travel can be counterbalanced by good preparation, including reading about the destination and, when possible, by identifying a local contact. The preparation of such at-risk travellers should include discussion of adaptation techniques and exercises, as well as discussion about alcohol and drug use. Hypnotics and anxiolytic medications can play a role in facilitating adaptation.

The immunocompromised traveller

Immunocompromised persons, including HIV-infected individuals, travel extensively. They do so for pleasure, business, family reasons or religious considerations. To tell a severely immunosuppressed person not to travel is unrealistic and does not take into consideration his or her own priorities. Travel medicine practitioners need to be aware of the most important risks, the preventive measures available and how to inform the potential traveller about the travel health risks and options. Preparing an immunocompromised individual for international travel requires attention to a number of important issues that, for the most part, are similar to those faced by any traveller with a chronic condition [1]. These considerations include:

- restrictions on crossing international borders
- vaccination requirements and their effectiveness and safety
- susceptibility to infections present at the destination
- accessibility of healthcare overseas and the possible need for medical evacuation home.

Vaccines

There are a very large and ever increasing number of vaccines available to protect travellers worldwide. Although most are safe for immunocompromised persons, some precautions are necessary with live attenuated vaccines (Tables 4.2 and 4.3). These include the yellow fever vaccine, the Bacille Calmette–Guérin (BCG) vaccine, the oral polio (Sabin) vaccine, measles, mumps and rubella (MMR) vaccine, oral typhoid vaccine, oral cholera vaccine and the new varicella vaccine. All inactivated vaccines can be administered to immunocompromised individuals if potential

Table 4.2 Vaccines generally to be avoided in immunocompromised travellers

Vaccine	Administration
BCG	Not recommended without exception
MMR	Administer if at risk and no evidence of immunosuppression
Oral ETEC/cholera	Not recommended
Varicella	May be considered if at risk and no evidence of immunosuppression Immunise close contacts of the immunocompromised traveller
Yellow fever	Administer if at risk and no evidence of immunosuppression
Oral typhoid	Use the injectable attenuated vaccine
Oral polio	Use the injectable attenuated vaccine Avoid for close contacts of the immunocompromised traveller
Herpes zoster (shingles)	Not recommended

Table 4.3 Vaccines safe for use in immunocompromised individuals

Vaccine	Notes
Diphtheria	–
European tick encephalitis	–
Hepatitis A and B	–
Hib	–
Human papilloma virus	–
Influenza and H1N1	–
Japanese encephalitis	Rare indications
Meningococcal	–
Pertussis	Prefer acellular
Polio, inactivated	–
Pneumococcal	–
Rabies	Pre- or post exposure
Tetanus	–

exposure to an infectious disease is likely or has occurred. Some of them, such as influenza and pneumococcal vaccines, are strongly recommended for such travellers. These vaccines represent no risk and are not contraindicated for travellers with HIV or AIDS. Some severely immunocompromised individuals may respond poorly to immunisation. Other strategies may thus be needed to protect them, such as passive immunisation with specific immunoglobulins, or preventive medication or rapid treatment in the event of an exposure. All immunisations should be given by medical personnel with special training and a good understanding of the principles of vaccination and the potential risks.

Severe complications have been reported after immunisation with live vaccines in immunosuppressed hosts.

Live vaccines

Live vaccines may not be indicated for all travellers. The travel health consultation should thus ascertain the exact itinerary and the possible indications. These vaccines are contraindicated in severely immunocompromised individuals. If such an individual is planning to travel to a yellow fever endemic area they should be recommended to change their itinerary or to follow strict bite avoidance measures against mosquitoes if the trip is unavoidable. When yellow fever vaccine is required to cross a border but no portion of the trip involves travel to an infected area, a certificate indicating a temporary contraindication to the administration of yellow fever vaccine can be considered. This certificate can be provided by authorised yellow fever centres. The traveller should be aware that, in the face of an epidemic, they could be denied entry to these countries if they are not immunised.

Bacille Calmette–Guérin (BCG) vaccine

The administration of BCG vaccine to immunocompromised persons is contraindicated because of its potential to cause disseminated disease [2].

Measles, mumps and rubella (MMR) vaccine

Six deaths have been linked with measles vaccine virus infection in immunocompromised individuals. Because of the severity of the disease, the vaccine should be administered to HIV-positive persons who are not severely immunosuppressed.

Oral polio (Sabin) vaccine (OPV)

OPV should never be given to any immunosuppressed individual, regardless of the level of immunosuppression, their household members or their close contacts. The risk of vaccine-associated paralytic poliomyelitis is increased by immunosuppression.

Varicella and shingles vaccines and varicella zoster immune globulin (VZIG)

Very limited data regarding the safety and efficacy of varicella vaccine or herpes zoster vaccine in immunocompromised adults are available, and no recommendation for use can be made for this population. There is no contraindication to the use of VZIG following exposure. The risk for severe disease from naturally acquired varicella and the potential benefit of vaccination should be evaluated. Vaccination may be considered (two doses, administered 3 months apart) for HIV-infected persons with CD4+T-lymphocytes count >200 cells/μl [3]. To decrease the risk of exposure to wild type varicella zoster virus, household contacts of immunocompromised persons should be vaccinated routinely.

Hepatitis A vaccine

Several inactivated and attenuated hepatitis A vaccines have been developed and evaluated in human clinical trials and in non-human primate models of hepatitis A virus infection [4]. However, only inactivated vaccines have been evaluated for efficacy in controlled clinical trials [5]. The vaccines licensed currently are Havrix (SmithKline Beecham Biologicals), Vaqta (Merck and Co., Inc.), Avaxim (Pasteur Merieux

Table 4.4 Precautions to be taken by immunocompromised individuals to avoid infection from potentially contaminated food or drink

- Cook meat and poultry to 73.8°C
- Wash fruit and vegetables thoroughly and carefully
- Reheat read-to-eat foods until steaming hot
- Use treated, boiled or bottled water
- Avoid:
  - raw or undercooked eggs
  - foods containing raw eggs
  - raw or undercooked (pink) poultry, meat or seafood
  - unpasteurised dairy products
  - soft cheeses
  - fountain beverages
  - ice cubes, if the source is unclear
  - raw oysters
- Avoid cross-contamination of foods

Connaught) and Epaxal (Berna Products), and all four are inactivated vaccines.

Environmental risks

Food and water

The risk of infection from contaminated food and water among immunocompromised persons may be increased during travel to developing countries. Those who do travel to such countries should be vigilant with regard to food and water precautions (Table 4.4). They should be advised that ice made with tap water, unpasteurised milk and dairy products (consumed commonly by travellers), and items sold by street vendors are usually unsafe. Foods and beverages that are generally safe include steaming-hot food, fruit peeled by the traveller, bottled (especially carbonated) beverages, hot coffee and tea, beer, wine and water brought to a rolling boil for 1 minute. Treatment of water with iodine or chlorine might not be as effective as boiling but can be used when boiling is not practical [2]. Water purifiers can be of some value.

Persons from developed countries who travel to developing countries are at substantial risk of hepatitis A infection [6]. All hepatitis A-seronegative individuals should be offered the vaccine or, if severely immunosuppressed, immunoglobulin.

Immunocompromised travellers should be educated and advised about the many ways that Cryptosporidium can be transmitted. Modes of transmission include:

- direct contact with infected adults, children in nappies and infected animals
- drinking contaminated water
- coming into contact with contaminated water during recreational activities
- eating contaminated food [2].

Travel medicine practitioners should advise immunocompromised travellers not to eat raw or undercooked eggs (including foods that might contain raw eggs, e.g. some preparations of Hollandaise sauce, Caesar and other salad dressings, and mayonnaise), raw or undercooked poultry, meat or seafood, or unpasteurised dairy products. Poultry and meat should be well cooked and should not be pink in the middle (internal temperature more than 73.8°C). All foods should be washed thoroughly before being eaten [2].

Cryptosporidium can also be transmitted by drinking contaminated water, ice made from contaminated tap water, fountain beverages served in restaurants, bars and theatres, and eating contaminated food [2]. Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Commercially packaged non-carbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (i.e. those that can be stored unrefrigerated on grocery shelves) are also safe [1]. Immunocompromised persons should avoid eating raw oysters because cryptosporidial oocysts can survive in oysters for more than 2 months and have been found in oysters taken from some commercial oyster beds.

Special topics

Restrictions on crossing international borders

Before scheduling a trip to a foreign country, HIV-infected travellers should be made aware that a number of countries screen travellers for evidence of HIV infection and can deny entry to seropositive individuals. In Canada, an unofficial list of entry requirements for crossing international borders may be obtained from the Laboratory Centre for Disease Control (see Additional Resources). Such requirements may change without notification, and verification with consulates or embassies is advisable.

Susceptibility to infection

Many infections encountered by travellers are associated with increased morbidity and mortality in immunocompromised persons. These individuals are more likely to have adverse reactions to drugs used to treat infection [1].

Malaria Malaria is a common and serious infectious disease, transmitted by mosquito bites from dusk to dawn. Personal protective measures are very effective in reducing the risk of

acquiring malaria. All travellers to endemic areas should be counselled about the use of insect repellent containing DEET on exposed skin and the use of bed nets, and advised to wear clothing that reduces the amount of exposed skin. An insecticide such as permethrin or deltamethrin on clothes and bed nets can reduce the risk further.

In many endemic areas, malaria prophylaxis should be taken to reduce the risk significantly, but never completely. Some of these medications are metabolised at the cytochrome P50, with Mefloquine being a good example. Drug interactions should thus be considered. Other drugs may contain a medication the HIV-infected traveller is already taking, at a different dose; for example, Malarone contains atovaquone, which is an active constituent of Malarone. Other medications could be used with acceptable efficacy for travellers with an already complicated therapy or those who have experienced severe side effects with previous changes in regimens. Azithromycin, rarely used in practice because of limited efficacy, and primarily cost, is an example. Doxycycline, increasingly used for chloroquine-resistant areas, can increase the risk of photosensitivity or of a recurrence of candidiasis.

Malaria can kill any healthy individual in just 3 days. As HIV-infected persons are more likely to experience fever as a symptom of an opportunistic infection, malaria could go unrecognised and lead to death or severe complications. Travellers and healthcare providers alike must consider the diagnosis of malaria in any febrile illness that occurs during or after travel to a malaria-endemic area [7].

Diarrhoea Prophylactic antimicrobial agents are not generally recommended for travellers; however, for immunocompromised travellers, antimicrobial prophylaxis may be considered, depending on the level of immunosuppression and the region and duration of travel. The use of fluoroquinolones such as ciprofloxacin (500 mg per day) can be considered when prophylaxis is deemed necessary. As an alternative (e.g. for children, pregnant women and persons already taking cotrimoxazole for Pneumocystis carinii pneumonia prophylaxis), co-trimoxazole might offer some protection against travellers' diarrhoea. The risk of toxicity should be considered before treatment with co-trimoxazole is initiated solely because of travel.

Antimicrobial agents such as fluoroquinolones may be given to travellers before departure, to be taken empirically (e.g. 1 g stat, followed, if diarrhoea persists, by 500 mg of ciprofloxacin twice a day for 3 days) should travellers' diarrhoea develop. Fluoroquinolones are generally avoided for anyone less than 16 years of age and pregnant women, and alternative antibiotics should be considered. Travellers should consult a physician if the diarrhoea is severe and does not respond to empirical therapy, if their stools contain blood, if fever is accompanied by rigors, or if dehydration develops. Antiperistaltic agents (e.g. diphenoxylate and loperamide) can be used to treat mild diarrhoea. They can also be used to supplement the antibiotic treatment if needed (for example, if the individual has a plane to catch). These agents should not be administered to travellers who have a high fever or who have blood in the stool.

Some experts recommend that HIV-infected persons who have Salmonella gastroenteritis should be given antimicrobial therapy to prevent extraintestinal spread of the pathogen. However, no controlled study has demonstrated a beneficial effect of such treatment, and some studies of immunocompetent persons have suggested that antimicrobial therapy can lengthen the shedding period. The fluoroquinolones, primarily ciprofloxacin (750 mg twice a day for 14 days), can be used when antimicrobial therapy is chosen [2]. Fluoroquinolones should not be used during pregnancy.

Special situations

Persons with physical disabilities, including mobility, hearing, seeing or cognitive problems, need more attention. They should be informed of the special services available to them in most hotels, airplanes or cruises. They should also know that they might not be accepted for some journeys, for example if they have severe visual problems they may not be able to travel alone on a cruise ship.

Contagious diseases

Infectious diseases that are airborne or easily transmissible by close contact are contraindications to travel and the intervention of public health officers may be required. In cases of doubt, always consult the national public health authorities for clearance of the traveller to travel before departure.

Insurance

All travellers should obtain health insurance for travel before leaving home. A signed contract is highly preferable to the glossy pamphlet of the cover offered to all carriers of a specific credit card. Pre-existing medical conditions do not preclude insurance cover; a higher premium can be offered, or the pre-existing condition may not be covered, but accidents and other problems would be.

A booklet produced by the International Association for Medical Assistance to Travellers (IAMAT) is a good resource for finding English-speaking physicians while travelling.

Conclusion

Fitness to travel is an abstract concept that is greatly influenced by the predisposition of the traveller. It requires the travel medicine practitioner to have a good knowledge of travel trends and the risks and efficacy of preventive measures to ensure the health of a traveller. It also requires the time and capacity to identify predisposing factors that can contribute to an increase or decrease in relative risks while travelling. An understanding of the medical facilities and services available abroad should also be taken into. As more and more travellers seek travel health advice only a few days before departure, the ability to meet their travel health needs through immunisations and medications with little time available is essential. No safety net can replace travel insurance providing coverage for medical and dental treatment abroad.

Above all, travel health practitioners and medical professionals as a whole should find the right balance between unduly scaring travellers and informing them of the appropriate risks. With very few exceptions, provided that a comprehensive travel health risk assessment has been completed, any traveller can undertake a journey safely.

References

1. Health Canada (1994) Statement on travellers and HIV/AIDS. *Canadian Medical Association Journal* **152**: 379–380.
2. USPHS/IDSA (1999) *Guidelines for the Prevention of Opportunistic Injections in Persons Infected with Human Immunodeficiency Virus*. US Public Health Service and Infectious Disease Society of America, Washington, DC, **48**(RR10), pp. 1–59.
3. Marin M *et al.* (2007) Prevention of varicella. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* **56**(RR04): 1–40.
4. D'Hondt E (1992) Possible approaches to develop vaccines against hepatitis A. *Vaccine* **10** (Suppl. 1), S48–S52.
5. Innis BL *et al.* (1994) Protection against hepatitis A by an inactivated vaccine. *JAMA* **271**: 18–34.
6. Steffen R *et al.* (1994) Epidemiology and prevention of hepatitis A in travelers. *JAMA* **272**: 885–889.
7. Health Canada (1997) Canadian recommendation for the prevention and treatment of malaria among international travellers. *Canada Communicable Disease Report* **23**: S5.

Additional resources

Aerospace Medical Association
Medical Guidelines Task Force: Airline travel, 2nd edition, 2003
http://www.asma.org/pdf/publications/medguid.pdf

International Diabetes Federation
1 reu Defacqz, B–1000 Brussels, Belgium
www.idf.org

National Health Services, UK
Fit for Travel: advice for travellers
http://www.fitfortravel.nhs.uk/advice/advice-for-travellers.aspx

Special Needs Travellers
Centers for Disease Control and Prevention
http://wwwnc.cdc.gov/travel/content/special-needs.aspx

Tropical Health and Quarantine
Population and Public Health Branch
Health Canada
http://www.hc-sc.gc.ca/pphb-dgspsp/tmp-pmv/prof_e.html

World Health Organization
International Travel and Health, Chapter 9: Special groups of travellers
http://www.who.int/ith/chapters/en/index.html

Chapter 5 Management of a travel clinic

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Introduction

Travel clinics of today have their roots in the public health and military medicine service clinics of the past, where preventive medicine strategies such as immunisations against vaccine-preventable diseases and precautions, prophylaxis and treatments for malaria, diarrhoea and sexually transmitted diseases were applied towards protecting the health of specific populations. During the decades following World War II, modern transportation and communication systems fostered a phenomenal growth in international travel for tourism, business and relief missions. The health concerns of increasingly large numbers of travellers gradually created the impetus to adapt traditional public health principles to meet the health needs of individual travellers. In many venues today, travel medicine goes beyond the traditional public health focus on hygiene and communicable diseases to encompass other aspects of health during travel: from jet lag, high-altitude illness and snakebites to personal safety, cross-cultural psychosocial issues, motor vehicle injuries and emergency medical evacuations. Since behavioural changes are often necessary in addition to medical interventions to prevent many of the health hazards associated with travel, a large component of travel medicine practice today focuses on health education for the individual traveller.

Travel clinic models

Given the many variations in health services available for travellers at diverse local, national and international locations, a consistent system for travel clinic nomenclature helps clients and colleagues easily distinguish among organisational models. In the descriptions that follow, travel clinic types are named on the basis of the level of services provided (Table 5.1). The services range from administration of travel immunisations only (travel immunisation clinics), to clinics where immunisations are accompanied by comprehensive trip health risk assessment, prescription of medications and extensive travel health advice (travel health clinics). Other travel clinics provide the services listed above, and perform pre-travel physical examinations and diagnostic tests that are often necessary for expatriate assignments, foreign work permits or fitness certifications for special activities, such as scuba diving or mountain climbing (travel medicine clinics). Such clinics also advise special travellers, such as those with impaired immunity or who have chronic health conditions or illnesses. The fourth kind of clinic is staffed by clinicians with special expertise in the diagnosis and treatment of tropical and exotic diseases, who provide consultation for travellers returning from travel abroad with serious or persistent medical problems (travel and tropical medicine clinics).

The clinical environment suitable for a travel clinic is determined by the anticipated scope of practice. Travel health services can be provided as an added feature in many settings, including public health clinics, private medical practices, occupational health clinics, student health centres and emergency departments, or can be organised as a dedicated travel clinic. Dedicated travel clinics may be operated as freestanding entities located in independent offices, multispecialty clinic buildings, medical centres and shopping centres, or even at international airports.

Travel clinic staff

Travel medicine clinics are often multidisciplinary patient care teams that include nurses, physician assistants/nurse practitioners/clinical nurse specialists and/or physicians [1]. Although travel medicine providers come from a wide variety of medical specialties such as internal medicine, family practice, paediatrics, occupational medicine, infectious diseases, tropical medicine, military medicine and

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Table 5.1 Travel clinic categories according to level of service

Travel clinic type	Services provided	Clinical providers[a]
Travel immunisation clinic	Travel immunisations (immunisation protocols)	RN
Travel health clinic	Travel immunisations (immunisation protocols)	RN
	Travel health advice	RN / CNS / ARNP / PA / MD / DO
	Prescription of travel medications	CNS / ARNP / PA / MD / DO
	Letters and travel documents	CNS / ARNP / PA / MD / DO
Travel medicine clinic	Travel immunisations	RN
	Travel health advice	RN / CNS / ARNP / PA / MD / DO
	Prescription of travel medications	CNS / ARNP / PA / MD / DO
	Letters and travel documents	CNS / ARNP / PA / MD / DO
	Counsel patients with special needs	CNS / ARNP / PA / MD / DO
	Physical examinations and forms	CNS / ARNP / PA / MD / DO
Travel and tropical medicine clinic	All services in categories above	CNS / ARNP / PA / MD / DO
	Diagnosis and treatment of illness in returned travellers, immigrants and refugees	

RN = registered nurse; CNS = clinical nurse specialist; ARNP = advanced registered nurse practitioner; PA = physician assistant; MD = doctor of medicine; DO = doctor of osteopathy.
[a]Clinical providers licensed in the US are used as example.

refugee/migration medicine, to provide travel medical care they need to have acquired the core body of knowledge in travel medicine. What brings this diverse group of practitioners together is a common interest in and dedication to assuring the mental and physical health of travellers before, during and after international travel; to provide travel medical care they need to have acquired the core body of knowledge in travel medicine.

The key challenge facing travel medicine as a unique medical specialty is to define the core body of knowledge that transcends the wide spectrum of health perspectives [2–7]. The internet has greatly heightened awareness of global health conditions in real time, and drives the need for timeliness and coordination of disease surveillance, advice to travellers in response to new and emerging health conditions abroad, access to medical care and pharmaceuticals across national boundaries, and cross-cultural communication related to health issues. The clinical group of the American Society of Tropical Medicine and Hygiene (ASTMH) has defined a core body of knowledge that encompasses both travel medicine and clinical tropical medicine, and sponsors a certification examination for physicians. The International Society of Travel Medicine (ISTM) also offers a similar certification for travel health providers, which serves as a benchmark for travel nurses and other healthcare providers in the field. This core body of knowledge can be acquired by completing diploma or masters level courses in travel and tropical medicine. The breadth of the knowledge includes specific travel-related geographic infectious and non-infectious illnesses and their prevention and potentially management. In addition to the knowledge, the providers should have enough experience (at least 10–20 travel medicine consults per week for 6 months of the year) to maintain the knowledge and be involved to regular continuing educational activities to keep abreast of new recommendations. The web resources of ASTMH and ISTM should be consulted for further details (*see* Table 5.2).

Staffing of individual clinics will vary according to the spectrum of services that are planned to be provided at that particular clinic (*see* Table 5.1).

Information resources

The first requirement for a travel clinic of any kind is to establish reliable and up-to-date information sources. Reliable and authoritative travel medicine publications of the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) often serve as official references for local standards of practice. Both organisations publish annual or biannual printed and online versions of their updated recommendations on advice and health information for international travel (*see* Table 5.2). Updates are published online as needed between the annual or biannual reviews. In 2006, the Infectious Diseases Society of America (IDSA) published guidelines for pre-travel

Table 5.2 Useful websites for travel clinics

Name of organisation	Website
American Society of Tropical Medicine and Hygiene (ASTMH)	http://www.astmh.org
Centers for Disease Control and Prevention (CDC)	http://www.cdc.gov
ProMED mail: the global electronic reporting system for outbreaks of emerging infectious diseases and toxins	http:// www.fas.org/promed
International Society of Travel Medicine (ISTM)	http://www.istm.org
World Health Organization (WHO)	http://www.who.org
The Committee to Advise on Tropical Medicine and Travel (CATMAT), Canada	http://www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/index-eng.php
Smartraveller: the Australian Government's travel advisory and consular assistance service	http://www.smartraveller.gov.au/
Health Protection Agency, United Kingdom	http://www.hpa.org.uk/
The Australian Government Department of Foreign Affairs and Trade	http://www.immunise.health.gov.au/
The British Foreign and Commonwealth Office:	http://www.fco.gov.uk
National Travel Health Network and Centre, UCLH NHS Foundation Trust	http://www.nathnac.org/
Faculty of Travel Medicine, Royal College of Physicians and Surgeons of Glasgow, Scotland	http:// www.rcpsg.ac.uk
World Sites Atlas	http://www.sitesatlas.com/
United Nations Maps	http://www.un.org/Depts/Cartographic/english/htmain.htm
The CIA Factbook for up-to-date country information	http://www.cia.gov/library/publications/the-world-factbook/index.html

recommendations for travellers[8]. These can be accessed from the IDSA website (www.idsociety.org).

Other national and regional public health entities produce advisories relevant to the health of travellers and should be consulted for country-specific guidelines. These include the Asia Pacific Travel Health Association (APTHA), the Australian National Health and Medical Research Council (NHMRC), Canada's Public Health Agency Travel Medicine Program guided by the Committee to Advise on Tropical Medicine and Travel (CATMAT), the China International Travel Health Association (CITHA), the National Travel Health Network and Centre in the United Kingdom (NaTHNaC), the Health Protection Agency (HPA) in the United Kingdom, the Taiwan Travel Health Association and others. Local public health departments and travel clinics affiliated with academic medical centres can also serve as resources for information and guidance.

There is a growing body of journals, periodicals, web-based resources (*see* Table 5.2) and books that serve as valuable references in a travel clinic [9–12]. A world map showing countries, major cities and international time zones, as well as a comprehensive world atlas giving elevations and physical characteristics of land masses within countries, are especially valuable for pre-trip assessments. Charts showing average temperatures and altitudes at destinations throughout the year are also helpful for planning.

The internet has a wealth of information that can assist the provider. Many commercial vendors offer software and web-based programs for a subscription to provide convenient, efficient and summarised information in travel clinics, particularly where the patient care operations are extensively computerised. The best way to become acquainted with these commercial products is to search the web, consult with or visit travel clinics where these programs are installed, or visit vendor demonstrations at professional meetings. In smaller clinic operations where subscriptions to commercial programs are not cost-effective, an excellent level of information can still be accessed on the CDC, WHO, Immunise Australia and NaTHNaC websites; and through participation in one of the list serve groups open to members of the ISTM and/or the ASTMH (*see* Table 5.2). The internet (for example a Google search) can be invaluable in locating smaller towns or cities that may not be easily recognised by name or to find an altitude of a lesser-known destination. Information about specific locations can also be found at websites such as World Sites Atlas, United Nations Maps link, Smartraveller (the Australian Government's travel advisory and consular assistance service), the British Foreign and

Commonwealth Office and The CIA Factbook for up-to-date country information (*see* Table 5.2).

Travel and tropical medicine clinics providing assessment, diagnosis and treatment for ill returning travellers will find that participation in clinical email discussion groups will augment and update the information found in standard textbook references. In addition to the discussion groups for members of the ASTMH and the ISTM organisations, the email postings of ProMED covering disease outbreaks and emerging infections worldwide can be very useful in the evaluation of post-travel patients. The ProMED subscription list is open to any interested party (*see* Table 5.2).

Travel clinic operations

Travel medicine services can be provided in almost any clinic space suitable for patient care. If the travel clinic is part of a larger organisation, space and support service requirements are less because of shared clinic functions, such as marketing and promotion, telephone and patient reception, appointment scheduling, patient registration, patient waiting room, medical records storage, secretarial and administrative support (including the ordering of clinic supplies and pharmaceuticals, data management and accounting), patient billing, payer (or insurance) relations and custodial services [13, 14]. For members of the ISTM there is an excellent online, detailed step-by-step resource for implementing and operating a travel clinic effectively.

Vaccine injections at travel immunisation clinics may be administered in multi-patient or group clinic settings if necessary, as most vaccines are now administered in the upper arm; privacy screens or curtains may be used for patients receiving injections of immune globulin in the gluteus muscle. However, a private room is necessary for patient interviews to conduct individual trip risk assessment and patient counselling, as sensitive topics may be discussed. Likewise, physical examinations require privacy, an examination table, the usual medical equipment and supplies, and, often, the help of a medical assistant. Thus, the clinical activities of some travel clinics require the use of dedicated patient examination rooms. Depending on a clinic's location, specific standards for licensure of patient care facilities may govern room dimensions, provisions for patient privacy, presence of a sink in the room for hand-washing, sanitation of medical equipment and linens, hazardous waste disposal and patient access to toilet facilities.

A clinic that administers travel immunisations (one-stop-shop clinic) has to determine the age range to be served (paediatric, adult, or both). Specific tasks for smooth operations of a travel immunisation clinic include the following.

1 Develop appointment guidelines:
   (**a**) develop an appointment triage system – decide if all patients will have the same time allocated or develop different time allotments based on complexity of appointment
   (**b**) develop a triage system for patients who see a physician (if physician is part of the clinic) or a nurse
   (**c**) develop appointments slots for subsequent boosters such as completion of hepatitis B series and others
   (**d**) develop time allocations for when and if a married couple or a family is seen together – based also on travel destination and patient history complexity
   (**e**) accommodation of last-minute travellers
   (**f**) availability for post-travel illness evaluation
   (**g**) develop a mechanism to mail patient health history intake form prior to coming to the clinic
   (**h**) develop a script for the appointment secretaries to communicate to the patients about possible lack of insurance coverage, and the need to bring specific itinerary details and prior vaccine records to the appointment.
2 Patient flow and educational materials:
   (**a**) develop the patient health history intake form
   (**b**) develop the procedure for obtaining and recording each patient's vital signs (consider a paediatric weigh station if children are seen in clinic)
   (**c**) establish age-appropriate vaccine protocols for each vaccine in use
   (**d**) develop or acquire patient education materials regarding common travel-related problems in English and in languages common in the region
   (**e**) information or reference for healthcare abroad in case of illness while travelling.
3 Vaccine management:
   (**a**) apply for status as an official Yellow Fever Vaccine Center
   (**b**) obtain supplies of the WHO *International Certificates of Vaccination* to serve as the individual traveller's official immunisation document
   (**c**) identify a process to document vaccinations in the *International Certificates of Vaccination*, the institutional records and national, state or local vaccine information systems
   (**d**) develop age-appropriate vaccine protocols for each vaccine in use and regularly update vaccine protocols to be used by nurses adapted to local regulations
   (**e**) establish patient consult and immunisation records
   (**f**) create updated age- and language-appropriate vaccine consent forms and information sheets
   (**g**) train staff in vaccine administration, scheduling and documentation of doses
   (**h**) set up a system to do an inventory of the available vaccines, including ordering, storing and documenting

incoming vaccines. Vaccine supplies should match the volume of patients seen in given clinic

(i) develop a system to track imminently expiring vaccines

(j) develop a system to handle vaccine shortages, including a need to batch patients to receive a specific vaccine in short supply (for example, the multidose [five doses] vial of yellow fever vaccine lasts only 1 hour once reconstituted, so in case of shortage of single-dose vials of the vaccine, patients need to be scheduled tightly to make optimal use of the multidose vial)

(k) provide alarm-enabled, temperature-monitored refrigerator for vaccine storage with an emergency electricity outage alarms. Establish a mechanism of management of vaccines should an outage occur. There should be an on-call list of the personnel on the fridge to contact in case of an emergency

(l) provide for safe disposal of needles, syringes and vaccine vials

(m) establish on-site capability for emergency medical care of a patient who develops acute anaphylaxis following administration of a vaccine

(n) develop a system for reminders for patients to complete their vaccine series and post-travel follow-up, such as a PPD after prolonged high-risk travel

(o) develop protocols for triage and care of patients who experience adverse side effects associated with immunisation

(p) establish a system to be able to contact patients in case of vaccine recalls.

4 Develop templates for letters commonly used in a travel clinic, such as:

(a) yellow fever or cholera vaccine waiver letter. Yellow fever vaccine waiver letter may be needed in Spanish language as well

(b) letter stating medical diagnosis and medications

(c) letter stating medical need to carry syringes, needles, injectable medications or devices such as continuous positive airway pressure (CPAP) machine

(d) missed appointment (for boosters etc.) letter reminding patient to either complete the series somewhere else if possible or to return to the clinic to complete as planned.

5 Other:

(a) process to handle phone calls during the work day

(b) a decision and a process to handle phone calls from overseas during off-hours if the clinic plans to provide that service.

6 Quality improvement:

(a) assess process, educational materials and other forms to adapt with changing needs and travel medicine standards of care.

Travel and tropical medicine clinics find that identifying reliable clinical laboratories that can perform advanced parasitic diagnostic tests, and pharmacies that are willing to stock or obtain antiparasitic drugs, is essential for patient care. Often, regional or national public health agencies can assist clinicians practising outside metropolitan areas in obtaining information about sources for the less common laboratory tests and drugs.

Depending on local requirements for licensure of healthcare providers and the scope of practice defined for each type of licensure, the travel clinic staff may consist of physicians, nurse practitioners or physician assistants, and/or specially trained registered nurses working with a physician or physician group.

Approach to trip risk assessment

The three basic topics

The three basic topics that should be covered during a travel clinic encounter are:

- immunisations for vaccine-preventable diseases
- medications for malaria chemoprophylaxis, as appropriate for the planned itinerary
- instructions for management and treatment of travellers' diarrhoea.

The advice given for each of these topics will be determined by individual medical history, the specific geographic destinations and activities planned at each.

All travellers should be asked to bring records of medical history, medication and specifically the previous immunisations with them. An old 'Certificates of Immunisation' form is ideal for assessing the current vaccine status of repeat travellers. If old immunisation records are not available at the initial clinic visit, then a systematic review of the routine (standard), the required and the recommended travel immunisations, combined with a knowledge of the patient's health status, previous travel and detailed itinerary (see below) for the new trip, will enable formulation of a travel immunisation plan. Occasionally, a patient's vaccine history may need to be obtained by calling the patient's primary provider(s), previously visited travel clinics (can be identified from the ISTM or ASTMH Travel Clinic Directories), state registries or the public health clinics (especially for immigrants and refugees). Serum antibody tests to determine immunity to specific vaccine-preventable diseases can be performed as needed if there is sufficient time before trip departure. Most commonly performed are hepatitis A, measles, mumps, rubella and varicella, particularly in immigrants. Others that can be performed when there is an absolute clinical indication include rabies serology (by rapid fluorescent focus

inhibition test [RFFIT] method), but this is done only in limited laboratories and it may take a long time for results to be available.

As mentioned earlier, many travellers' ailments are not vaccine-preventable. The healthcare provider in a travel immunisation clinic has an opportunity and an obligation to advise the traveller if further pre-travel health measures beyond immunisations are prudent for the planned itinerary – even if this might necessitate an additional pre-travel clinic visit with another provider or at another clinic. An example is evaluating a patient with a chronic lung or cardiac condition for safe high-altitude travel.

The selection of malaria chemoprophylaxis and the need to employ additional precautions to decrease the risk of malaria infection are determined by the age and health status of the traveller, history of drug allergies or drug intolerance, and anticipated patient compliance with the recommended regimen. Recommendations on the drug of choice for a given malaria risk assessment may vary from country to country and depend somewhat on which drugs are approved, licensed and marketed in the country about which travel advice is being given.

Traveller education on the relative advantages and disadvantages of the various malaria drug regimens and the compliance issues is often a time-consuming process. The relative risks of adverse drug reactions with a given antimalarial drug regimen must be balanced against the risk of malaria infection when a suboptimal regimen is selected. Traveller acceptance of malaria chemoprophylaxis recommendations will be influenced by dosing interval: weekly (chloroquine, mefloquine) versus daily (doxycycline, primaquine, atovaquone plus proguanil [Malarone]). Other factors include duration of post-travel chemoprophylaxis, i.e. 1 week (primaquine, Malarone) versus 4 weeks (chloroquine, doxycycline, mefloquine), after leaving the endemic area and last but not least the total cost of one drug regimen versus another for the recommended duration of therapy. Travellers also need to understand the importance of not discontinuing or switching regimens while travelling, except as advised by knowledgeable healthcare professionals, despite well-intentioned warnings and advice from friends and fellow travellers. The emergence of strains of chloroquine-resistant *Plasmodium falciparum* (CRPF) and multidrug-resistant malaria, and widespread publicity in the lay press about adverse side effects associated with mefloquine (Lariam), one of the highly efficacious drugs that may be used for prevention of CRPF, add to the challenge of giving advice on malaria chemoprophylaxis.

Travellers' diarrhoea is a common and well-known scourge of international travel, and a leading motivation for travellers to seek pre-travel health advice. Questions about vaccines for diarrhoeal diseases, preventive therapy with probiotics, primary prophylaxis with bismuth subsalicylate or antimicrobials, and advice on the safety of food and water at their destination(s) are common. International travellers need clear instructions about how to select and use oral rehydration fluids, bismuth subsalicylate, probiotics and antimotility drugs such as loperamide, alone or combined with single-dose or short-term antimicrobial therapy as self-treatment if stricken by travellers' diarrhoea. Patient care instructions about signs and symptoms indicating a need for professional medical care are also important.

Emerging drug resistance among enteric pathogens to antimicrobials commonly used in the treatment of travellers' diarrhoea (trimethoprim plus sulfamethoxazole, ciprofloxacin and others) fuels the search for new approaches for prevention and treatment of travellers' diarrhoea. Highly efficacious vaccines against common forms of travellers' diarrhoea and the potential benefits from alteration of intestinal microecology are two areas of continuing research.

Health status of the traveller

The travel clinic intake form records age, place of birth, general health status, allergies to medications, vaccines/vaccine components or other substances, prior residence overseas and/or international travel, general health (acute or chronic illness, disability, pregnancy or planned pregnancy, lactation), list of medications taken on a regular basis (both prescribed and over-the-counter), vitamins, herbal preparations and dietary preferences.

Review of itinerary

Dates of trip departure and return home, and a list of interim destinations with anticipated dates at each destination, plus the accommodations and activities at each destination should be the first items on the patient intake sheet. These data are needed to determine the time available to do pre-travel immunisations and to calculate appropriate supplies of malaria chemoprophylaxis, medications for travellers' diarrhoea and other drugs to be included in the travel medicine kit, and to assess the potential health risks of the given itinerary.

In terms of health risks, multiple destinations add to the complexity of pre-travel preparation and planning because of varying health regulations and environmental conditions. Hygiene, sanitation and insect control are more challenging in a tropical climate compared with a temperate climate. As travellers go from urban to rural to remote locations within a country, access to organised healthcare, in case of an emergency, and telecommunications, to indicate the need for emergency evacuation, become more and more difficult. When the duration of a trip is prolonged, the

chance of a traveller becoming ill while still away from home, with the need to consult unfamiliar medical systems, is more likely than with a shorter trip because many of the common diseases of travellers have short incubation periods (<3 weeks).

Learning the details about the anticipated style of travel, such as mode of transportation, accommodations, level of contact with local residents and living conditions, may suggest other topics for advice that might benefit the traveller; for example, hazards of rural travel, vector-borne diseases (besides malaria), animal bites, tuberculosis, sexually transmitted infections and nutritional concerns. Identifying the purpose of travel, such as tourism, educational or cultural exchange, missionary work, volunteer work, political action, competitive sports, expedition, fieldwork, expatriate assignment, etc., can also highlight special exposures that the traveller can prepare for. Special travel health advice is needed for travel during pregnancy, travel for healthcare delivery or medical tourism especially in context of bloodborne pathogen and TB exposure, travel with infants and children, travel with medical conditions, HIV-infected travellers, travel with physical disabilities, senior travel, and adventure and wilderness travellers.

Patient information brochures

One of the challenges of the travel clinic encounter is to impart the large amount of travel health advice and information applicable to a given trip in a way that can be remembered by the patient within the time allocated for the travel clinic encounter (typically 30–60 minutes). Having patient information brochures, pre-printed prescriptions and printed instructions on what to do for vaccine-associated side effects saves significant time during the travel clinic appointments. The printed materials enable multiple providers to communicate the advice on each relevant topic and provide prescriptions according to the practice standards determined for the given travel clinic. Health topics that have proved useful in the University of Washington and Mayo Clinic travel clinics over the years include the following.

- Summary of adverse side effects of travel immunisations and instructions on when and how to call for help.
- Destination country information.
- Malaria: symptoms, prevention and post-travel evaluation for fever.
- Insect precautions and repellents.
- Food and water precautions.
- Travellers' diarrhoea management and self-treatment.
- Hepatitis A and B and other vaccines for the patient's travel destination.
- Sexually transmitted infections.
- Sun exposure precautions.
- High-altitude illness.
- Dengue fever.
- Swimming and beach precautions, including prevention of schistosomiasis.
- Travelling with children.
- Travel health and medical evacuation insurance.
- Travel medicine kits.

Conclusion

As international travel continues to become more commonplace in the lives of ordinary citizens all over the world, travel clinics continue to gain recognition among the general public and healthcare providers for their unique role in promoting the health and safety of travellers. Data from epidemiology and surveillance studies have provided the direction for the content of travel medicine practices to date. As data from evidence-based outcomes studies from current and future clinical investigations become available, it is to be expected that the practice of travel medicine will evolve in response to a better understanding of the interventions that lead to significant reduction in disease and injury among international travellers.

References

1. Tempelman-Kluit A (1996) Private medical clinic for travellers fills a niche in Vancouver. *Canadian Medical Association Journal* **154**(5): 697–698.
2. Jong EC and Southworth M (1983) Recommendations for patients traveling. *Western Journal of Medicine* **138**(5): 746–751.
3. Hargarten SW *et al.* (1991) Overseas fatalities of United States citizen travelers: an analysis of deaths related to international travel. *Annals of Emergency Medicine* **20**(6): 622–626.
4. Hill DR and Behrens RH (1996) A survey of travel clinics throughout the world. *Travel Medicine* **3**: 46–51.
5. Dardick KD and Baker ME (1997) Travel medicine and travel clinics, US and Canada. In: Steffen HDR (ed.) *Textbook of Travel Medicine and Health* pp. 34–39. Decker, Hamilton, ON.
6. Reid D and Keystone JS (1997) Health risks abroad: general considerations, in *Textbook of Travel Medicine and Health* (ed. HDR Steffen), Decker, Hamilton, ON, pp. 3–9.
7. Ryan ET and Kain KC (2000) Health advice and immunizations for travelers. *New England Journal of Medicine* **342**(23): 1716–1725.
8. Hill DR *et al.* (2006) The practice of travel medicine: guidelines by the Infectious Diseases Society of America. *Clinical Infectious Diseases* **43**(12): 1499–1539.
9. Keystone JS *et al.* (2008) *Travel Medicine*, 2nd edn. Mosby Elsevier, Philadelphia, PA.

10. Jong EC and Sanford CA (eds) (2008) *The Travel and Tropical Medicine Manual*, 4th edn. Saunders Elsevier, Philadelphia.
11. Jong EC (1999) Travel immunizations. *Medical Clinics of North America* **83**(4): 903–922.
12. Jong E and Zuckerman J (eds) (2004) *Travelers' Vaccines*, 1st edn. BC Decker, Hamilton, Ontario.
13. Shaw M (2006) Running a travel clinic. *Travel Medicine & Infectious Disease* **4**(3–4): 109–126.
14. Hill DR (2008) Starting, organizing, and marketing a travel clinic. In: Jay S *et al*. (eds) *Travel Medicine*, 2nd edn. Mosby Elsevier, Philadelphia, PA.

Section II
Infectious diseases and travel

Chapter 6 Epidemiology and surveillance of travel-related diseases

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Introduction

From being treated as a mere hobby of interested practitioners, travel medicine has developed into a serious medical discipline. Counselling in this field can draw on a growing wealth of evidence. Studies on various travel health risks have multiplied in the past few years: while PubMed list only 447 entries for 'Travel medicine' in the years 1980–89, 961 are listed for1990–99, and 3,588 for the time from 2000 to November 2009 [1]. It was recognised quite early on that local disease information from travel destinations was not sufficient for assessing travel-associated health risks. Travellers behave differently to inhabitants of travelled regions and thus tend to have other health risks. An increasing series of studies aimed directly at the various populations of travellers are being performed and are yielding information that has already changed travel medicine practice profoundly. Instead of assessing health risks by deducting from information gained from other populations, health professionals can now draw on results from studies that are concerned directly with the traveller. They are assisted increasingly by networks that collect and provide updated information. In the United Kingdom, the National Travel Health Network and Centre (NaTHNaC) has been specifically created by the government to promote clinical standards in travel medicine with the goal of 'protecting the health of the British traveller' [2].

While surveillance of infectious diseases has a long history, surveillance of imported diseases in travellers has started comparatively recently. Most systems are based on national notification schemes that are diagnosis-oriented. These conventional surveillance programmes largely depend on reporting to and then by public health departments and laboratories. Direct contact with the traveller by the person doing the reporting is an exception. National systems of infectious diseases surveillance generally focus on complete coverage. The potential advantage of this approach is that no cases are overlooked. In reality, however, compliance with notification regulations is very limited. Estimated coverage rates at or below 50% are the norm rather than the exception. The lack of motivation among those requested by law to report is one of the major stumbling points for traditional surveillance systems.

In addition to systems aiming at complete coverage, an increasing number of national and international sentinel networks are being established. The use of sentinel sites has the disadvantage that complete coverage cannot be achieved. However, a prudent selection of members can ensure that a sentinel network produces representative information. In general, sentinel networks consist of voluntary members who are more focused on surveillance. Thus, information flow is often faster than in systems that are aiming at complete coverage. Examples for this are multinational networks such as FluNet, the WHO global influenza network [3] and the European Legionellosis Surveillance Scheme (ELSS) [4].

Increased awareness of emerging infectious diseases has fostered the creation of syndrome-based surveillance networks. They work almost exclusively in sentinel settings. Unlike traditional notification systems, their aim is not to collect information on pre-defined diagnosis. This type of network rather tries to collect open, possibly even non-standardised information in order to detect new outbreaks and emerging pathogens within a short time. Possibly the most ambitious project of this type is the US Department of Defence Global Emerging Infections system (DoD-GEIS) [5]. Clinical sentinel networks represent another broadening of conventional surveillance programmes. The clear advantage of these systems is that the persons reporting the requested data have seen the travellers themselves and can relay first-hand information. Several provider-based sentinel networks have been implemented during recent years, in particular in the US, as part of a national response plan against emerging infectious diseases [6, 7]. The first sentinel surveillance effort focusing explicitly on travellers was

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Geosentinel, by design a global network that attempts to capture emerging infectious diseases [7].

The lack of surveillance data for imported infectious diseases in Europe prompted the foundation of the European Network on Imported Infectious Disease Surveillance (TropNetEurop), which focuses on the surveillance of imported diseases in travellers [8]. This is a clinician-based sentinel network. The network is designed to effectively detect emerging infections of potential regional, national or global impact at their point of entry into the domestic population. Sentinel surveillance reporting is carried out by participating sites using a standardised and computerised reporting system. Immediate transmission of anonymised traveller and laboratory data to the central database assures timely detection of sentinel events. Membership is voluntary and self-selected by participating centres and monitored by the steering committee of the network. Although the organisation of the network does not guarantee a representative data collection for Europe, most major referral centres of the continent are represented. Within a very short time, it has grown to 58 members in 17 countries, which represent the majority of centres of excellence for imported infections on the continent. Network members oversee approximately 57,000 travellers annually, making it the largest infectious disease sentinel network worldwide. Although focusing on diagnosis-based reporting on the forefront, TropNetEurop is actively encouraging reporting of unexpected events and syndromes. As will be discussed, the network has been very successful in detecting outbreaks of emerging diseases in the past and has thus proven its value as an additional surveillance tool [9].

Systematic observations

At least for large referral centres, reporting of all travellers seen by a sentinel site is clearly an overwhelming task if not supported financially. Thus, TropNetEurop settled on regular reporting of only three disease entities: malaria, dengue fever and schistosomiasis. Concentrating on this very limited amount of reports eased the effort for all member sites while still keeping a steady flow of reports that provide valuable information in monthly bulletins that are mailed to all members and, in abbreviated form, to other interested health professionals outside the network [8].

Malaria

Results following the collection of reports of malaria showed that, depending on the regional impact of immigrants and the amount of travel in the local population, data from national sources in Europe can be heavily skewed towards one or the other group [10]. Judging from the data provided by national systems of disease notification, TropNetEurop covers approximately 10% of all malaria travellers seen in Europe [10, 11]. Review of the reported data on falciparum malaria showed that West Africa contributed by far the most malaria travellers to TropNetEurop sites: 68.2% of all immigrants and 58.8% of Europeans were infected there [10]. Relatively fewer immigrants and more tourists were infected in East and Southern Africa. Reports from the World Tourism Organisation show that only 0.6–2.4% of European travellers to potentially malarious areas chose West Africa as a destination [12, 13]. This suggests a comparatively high relative risk of acquiring falciparum malaria in West Africa. In comparison, WTO reports that 16–21% of travellers from the same collective visited Southeast Asia. As only very few travellers with falciparum malaria were reported from this area, the relative risk appears to be very low. These findings are comparable to previous studies from various non-endemic countries [14–16]. Only a minority of travellers with falciparum malaria took prophylaxis or combination prophylaxis appropriate to the drug resistance situation of malaria at the respective destination [17]. It is probable that a high percentage of the malaria cases reported could have been avoided by taking an appropriate malaria prophylaxis regimen. Information like this can be applied when giving health advice to travellers.

The course of illness with falciparum malaria tends to be milder in immigrants compared with Caucasians, although available data are not sufficient to show clear differences (Table 6.1). A large number of travellers of the former group were semi-immune inhabitants of malarious areas, while

Table 6.1 Signs and symptoms in Europeans and Immigrants with falciparum malaria [10], used with permission from Oxford University Press

Symptom	Immigrants (n = 790)	Europeans (n = 869)
Fever	603 (76.3%)	704 (81%)
Headache	388 (49.1%)	432 (49.7%)
Fatigue	189 (23.9%)	302 (34.8%)
Myalgia, arthralgia	136 (17.2%)	202 (23.2%)
Diarrhoea	77 (9.7%)	121 (13.9%)
Vomiting	96 (12.2%)	104 (11.9%)
Respiratory complaints	21 (2.7%)	30 (3.5%)
Neurological complaints	10 (1.3%)	22 (2.5%)
Skin affections	10 (1.3%)	11 (1.3%)
Otitis	56 (7.1%)	8 (0.9%)
Other	157 (19.9%)	153 (17.6%)
None	49 (6.2%)	0

Multiple entries possible.

European travellers were all non-immune. It is notable, however, that 3.7% of immigrants developed complications during their clinical illness. While this percentage is lower than in European travellers (6.3%), some immigrants were critically ill when presenting at the reporting centres. Immigrants who plan to visit their home country after several years may have only a limited perception of the travel health risks and necessary prophylactic measures in order to address their travel health needs. This is a group that is underrepresented in travel clinics and should be sought actively. Perhaps surprising at first, a group that appears to have a higher-than-average risk for complications with falciparum malaria are business travellers. Judging from the reports to TropNetEurop, this group tend to seek pre-travel counselling less frequently, to follow advice less reliably and, if symptomatic, to seek medical help later than other travellers.

While analysing falciparum malaria in travellers, it was shown conclusively that increasing age is a risk factor for severe falciparum malaria in non-immune travellers [18]. Altogether, 1,181 non-immune travellers with falciparum malaria met the study's inclusion criteria. Results from adjusted analyses, controlling for potential confounding, showed that the risk of dying from falciparum malaria (OR 1.85, CL95% 1.30–2.62), experiencing cerebral malaria (OR 1.66, CL95% 1.31–2.12) or severe disease in general (OR 1.32, CL95% 1.14–1.53) or being hospitalised (OR 1.21, CL95% 1.06–1.39) increased significantly per decade of life (Table 6.2). Comparing elderly (60 years and older) travellers with younger travellers showed that case fatality was almost 6 times higher among elderly travellers (OR 5.74, CL95% 1.78–18.47). Cerebral complications occurred three times more often (OR 3.29, CL95% 1.20–9.01). Antimalarial chemoprophylaxis was significantly associated with lower case fatality (OR 0.17, CL95% 0.04–0.74) and less frequent cerebral complications (OR 0.44, CL95% 0.20–0.96). The study provided evidence that falciparum malaria is more serious in older travellers, and demonstrated that clinical surveillance networks are capable of providing quality data for investigating rare events or diseases.

Dengue fever

Analysis of the data on dengue fever in travellers showed that the majority were Europeans who travelled for tourist reasons [19]. Asia contributed the most dengue travellers to TropNetEurop sites: 23.3% visited Southeast Asia, 22.9% the Indian subcontinent and 6.5% Indonesia. Numbers were slightly lower for the Americas, which contributed a total of 38.2% of all travellers. One case was reported in a traveller who had returned from Hawaii in 2000, heralding the later outbreak of dengue fever on Maui [20]. Reports from the World Tourism Organization show that 16–21% of European travellers travelled to Southeast Asia and only 6–8% to India [12, 13]. This suggests a high relative risk of acquiring dengue fever in the latter region, while numbers from Southeast Asia appear to reflect the high number of tourists to that area. The low number of infections that were acquired in Africa is consistent with all previous epidemiological data [21–29]. Importation of dengue fever into Europe shows a seasonal pattern that most likely reflects the travel habits of European tourists rather than true variations in disease activity.

The early years of reporting to TropNetEurop saw a steady annual increase in the total number of reported cases of dengue per year. This reached a peak in 2005 and a slight decline has been observed since then. Changes in the local

Table 6.2 Age-specific frequency of outcomes of severe falciparum malaria [19], used with permission from Oxford University Press

		Fatal cases	Cerebral complications (B50.0)	Other complications (B50.8)	Hospital admissions*
Age group	**Number of travellers**	**%**	**%**	**%**	**%**
10–19 years	50	0.0	0.0	4.0	70.0
20–29 years	290	0.7	1.0	5.2	79.0
30–39 years	369	0.5	1.9	5.4	79.7
40–49 years	225	2.2	6.2	7.6	81.8
50–59 years	169	2.4	4.7	9.5	85.2
60–69 years	56	3.6	5.4	3.6	73.2
70–79 years	20	10.0	10.0	20.0	95.0
80–89 years	2	0.0	0.0	0.0	100.0
Total	1,181	1.4	3.1	6.4	80.3

*Missing values in 39 cases.

Table 6.3 Signs and symptoms in 294 Europeans and immigrants with dengue fever [20]

Symptom	N	%
Fever	236	80.3
Headache	158	53.7
Fatigue	115	39.1
Myalgia, arthralgia	113	38.4
Exanthema	79	26.9
Diarrhoea	54	18.4
Vomiting	22	7.5
Respiratory complaints	17	5.8
Neurological complaints	7	2.4
Psychologic complaints	5	1.7
Otitis	22	7.5
Genitourinary	3	1.0
Other	30	10.2
None	21	7.1

Multiple entries possible.

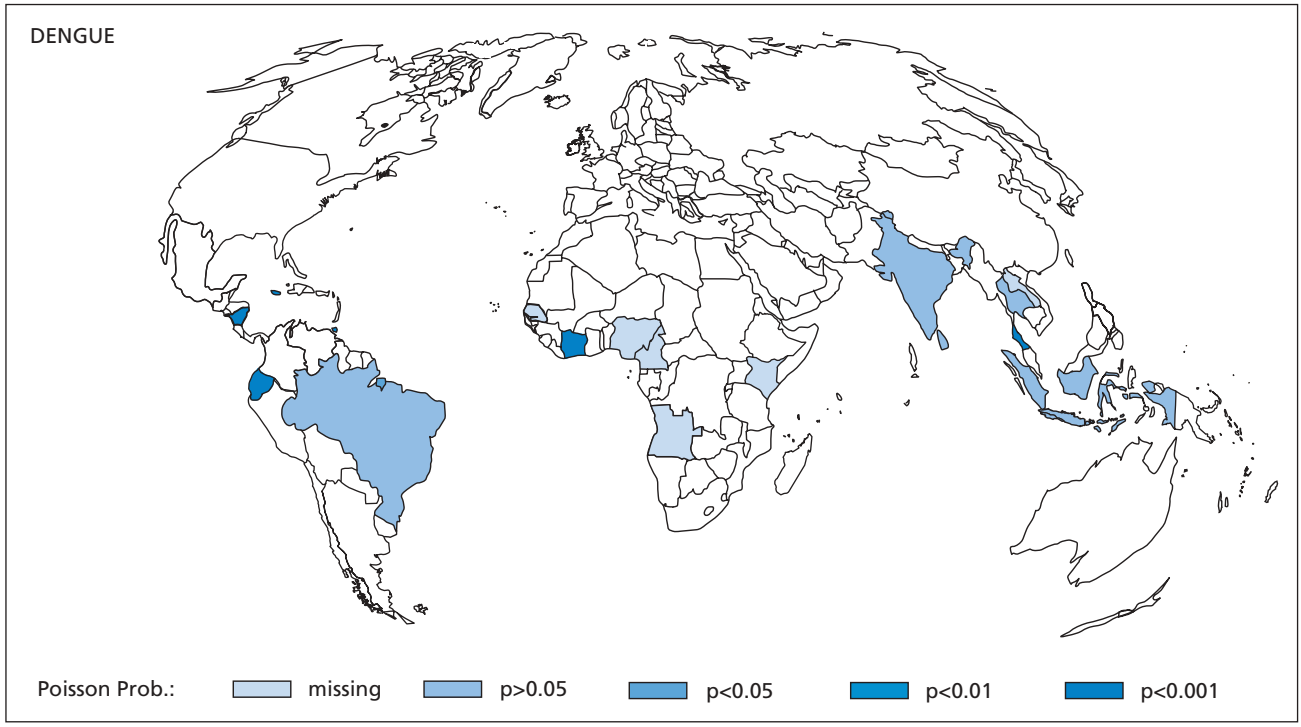
activity of dengue have been considerable: the proportion of cases in travellers returning from Southeast Asia increased from 29% in 1999 to 66.1% in 2002 and decreased again to 43.2% in 2008. A similar tendency was observed in case reports from India (14.5% in 1999 to 21.1% in 2001 and 11.9% in 2008), while case reports from the Americas decreased. This may reflect changes in travel patterns, but reports from the World Tourism Organization do not indicate major shifts in the travel activities of Europeans away from the Americas and towards Asia [12, 13]. More likely, these numbers reflect the activity of dengue in the regions that are visited by European travellers. Thus, an increase of case reports in travellers who have returned from an endemic area can serve as an early indicator for increased disease activity. Symptoms commonly associated with dengue, such as fever, myalgia, arthralgia and exanthema, can be helpful in making the diagnosis when present, but missing typical symptoms does not exclude infection (Table 6.3). Most dengue cases in this group were symptomatic and they presented with fever and headache as well as other symptoms including myalgias, fatigue, skin problems (exanthema) and diarrhoea.

Risk estimates

As shown above, sentinel surveillance in travellers is hampered by the lack of true denominator data. It is very difficult, if not impossible, to obtain reliable estimates regarding the travel activities of the population contributing to this data. This problem is increased by the contribution of asylum seekers and refugees coming from other countries into the area where surveillance is being established. Thus, a large number of travellers returning with falciparum malaria from West Africa may only reflect increased travel activity to that area and not an increased risk for infection. Clinical sentinels are able to recognise disease importation from countries where this usually does not occur. However, their ability to detect increased risks of infection in endemic countries is very limited. This is because importation of tropical diseases is not a frequent event and the number of potential countries with infection is large, so that even large clinical units usually observe too few cases of disease importation from single countries to be alerted to an increase in infection. For example, if a unit on the basis of a monthly average observes one case of malaria importation from an endemic country, even a doubling of infections from that country will not raise suspicion, because small numbers are subject to large chance variation. Detection of unlikely notification increases from single endemic countries requires a minimum number of cases. For tropical diseases, this is only feasible when combining surveillance data from several sentinel units.

As a network of clinical sites that are also responsible for pre-travel counselling, TropNetEurop has a strong interest in detecting increased risks of infection in tourist countries promptly. Therefore pooled TropNetEurop surveillance data are screened for unexpected notification increases at monthly intervals. As data from imported disease surveillance lack a true denominator, unexpected notification increases may be caused by increased transmission rates, changes in travel or migration patterns, or altered notification behaviour, e.g. triggered by outbreak rumours. Thus, unexpected increases are certainly no proof of an increased risk of infection in tourist countries, but rather should be interpreted as a warning signal to focus attention on any significant observations that should trigger further investigation. Since further investigations are time-consuming, a priori exclusion of non-significant signals saves resources and improves vigilance. This is especially important when disease importation from several dozen potential countries of infection is being monitored, and when attention needs to be focused in order to prevent the relevant findings being drowned by the multitude of information.

To screen TropNetEurop data for unexpected notification increases, a software tool was developed for observing recent case numbers and comparing those with numbers from previous reference periods. Poisson probabilities, expressing the likelihood of detecting as many as the recently observed cases or more compared with the expected number of cases from the past, are calculated for each country and presented in tables and maps. On the maps, levels of significance are indicated by different coloration. To account for



The probabilities express the likelihood of detecting as many or more cases over the previous 6 months, given case expectations from the same period one year ago. Dark areas indicate unlikely observations. Missing indicates that cases were observed in the past reference, but not in the recent observation period.

Figure 6.1 Result map from TropNetEurop screening for unexpected increases of dengue fever notifications in spring 2002.

the multiple-testing situation, observations are considered unlikely if the Poisson probability is lower than 0.001.

An example of the described screening approach given in Figure 6.1 clearly demonstrates the screening results from spring 2002 that triggered the detection of an outbreak of dengue fever among tourists in Thailand. Altogether, 37.5% of the dengue infections observed within a period of 6 months were imported from Thailand. Compared with the same period the previous year when the country accounted for only 11.1% of the cases, the recent observation was unlikely and therefore may have heralded a true increase in risk. Further signals were received from the Cote d'Ivoire and some Central American and Caribbean countries. However, those signals were caused by single case observations that could not be considered because the countries had not contributed cases to the database in the previous reference period.

Detection of sentinel events

TropNetEurop has demonstrated on several occasions that sensitive detection of sentinel events in travellers can lead to outbreak detection.

Falciparum malaria in the Dominican Republic [30]

Like most countries in the Caribbean, large parts of the Dominican Republic are considered as low-risk areas for falciparum malaria [31]. In general, only border regions with Haiti and provinces in the north-west of the country have been associated with endemicity. This pattern was reversed a few years ago: starting with an index case in June 1999, 12 additional European travellers presented with falciparum malaria acquired in the Dominican Republic during the period from November 1999 to February 2000. The travellers were identified and reported within TropNetEurop. The travellers were all on package tours to the Dominican Republic; two were Spanish, one was Austrian and the rest were German nationals. All travellers had travelled to Punta Cana, a town situated at the eastern tip of the Dominican Republic, or nearby beach resorts. This area had not been identified as being malarious, and in accordance with almost all European recommendations at that time, none of the travellers took malaria chemoprophylaxis. Similarly, malaria post-exposure prophylaxis was not adminsitered. Within 1–2 weeks of returning from their journey, travellers presented to their

general practitioner or at emergency departments with fever, and were admitted after diagnosis of falciparum malaria was established. Drug treatment proved successful in all travellers and the clinical course was uneventful.

The clustering of cases during a comparatively short time appeared to indicate a change in the epidemiological situation and might herald further outbreaks among tourists during future travel seasons. According to information from the Malaria Department in the Dominican Republic, there had been an increase in malaria in 1999 following hurricane George with 3,003 cases reported up to 20 November, an increase over the 2,000 cases for the whole of 1998. In the east of the country, an outbreak of falciparum malaria among the local population was noted and traced back to building activities on behalf of the tourist industry. Here, Haitian builders were brought in and some of them imported *P. falciparum* strains. With anopheline vectors present and abundant breeding sites in that area, transmission of falciparum malaria was technically easy [32]. No reports were received of infections among tourists from other nations, especially the United States, Canada and the United Kingdom. This may reflect a different use of malaria chemoprophylaxis or exposure prophylaxis for travel to the Dominican Republic. The discussion of the index case among the member sites of TropNetEurop triggered increased awareness within the network and led to the reporting of other cases within days of presentation in travellers who might otherwise have gone unnoticed since they presented at different hospitals all over Europe.

African trypanosomiasis from Tanzania [33]

African trypanosomiasis (sleeping sickness) is a severe protozoan infection (*Trypanosoma brucei*), usually spread from infected animals and humans by the tsetse fly. Although the World Health Organization is reporting an increase in its incidence in Africa, African trypanosomiasis has remained a rare, but well-documented cause of fever in travellers returning from endemic areas. Prompt, appropriate therapy has resulted in favourable outcomes for many travellers in Europe. Game parks in Tanzania have long been considered to be low-risk areas for African trypanosomiasis [34]. However, in February 2001, two index cases, followed by an additional six European cases and one South African, presented with trypanosomiasis [35]. The travellers were identified and reported within TropNetEurop. All the travellers had travelled to the Tarangire and Serengeti National Parks. This area has been identified as being endemic for African trypanosomiasis; however, case incidence among Tanzanian and foreign nationals has been exceedingly low in the past few decades.

During their journey or briefly after their return, travellers presented with fever at their general practitioner or emergency departments. Diagnosis was established by thin and thick blood film and although specific medication was difficult to obtain, drug treatment proved successful in all but one traveller, even though three travellers presented with multi-organ failure. The temporal clustering of imported cases suggested a change in the local epidemiology and could have heralded future cases in tourists during the travel season. The reaction of the Tanzanian authorities upon being informed, involved strengthening of the installation of insecticide impregnated targets in Serengeti around roads, lodges, staff quarters and campsites. The effect of this initial programme was a dramatic decline in tsetse flies in the Serengeti during the second half of 2001. Drugs for treatment of African trypanosomiasis were extremely difficult to obtain, and in some of the European travellers treatment with suramin was only possible after informal help from member sites of the network.

Falciparum malaria in illegal Chinese immigrants [36]

Between November 2002 and March 2003, 17 cases of malaria among illegal Chinese immigrants were observed in seven hospitals in central and northern Italy (15 cases of *Plasmodium falciparum*, one case of *P. malariae* and one mixed infection *P. falciparum/P. malariae*); one traveller died. Prior to 2000, *P. falciparum* malaria had not been reported in Chinese immigrants, despite many thousands living in Italy and other parts of Europe [10]. Although malaria is still endemic in parts of China, mostly at a low level of transmission [37], the major species is the benign strain of malaria, *P. vivax*. *P. falciparum* transmission is confined to provinces bordering Lao PDR and Vietnam. All travellers reported a stay varying from some days to several months (3 to 9) in an African country during their travel to Europe. Some had already fallen ill while in Africa. Others had reportedly died from 'fever' before reaching Europe. Malaria in Chinese immigrants highlighted a new route being used by traders of 'human cargo', which bypassed the traditional route through Central Asia and Eastern Europe. A single country, Cote d'Ivoire, was the transit country for almost all travellers. The clustering of cases, despite variable time in transit, suggests that the illegal immigrants arrive in Europe in groups when the entry conditions are more favourable. Although Italy was the final destination, at least some entered through France, which also reported cases of *P. falciparum* in Chinese immigrants (Legros F, Centre National de Référence de l'Epidémiologie du Paludisme, France, Personal communication).

Falciparum malaria in travellers to Gambia

During summer and autumn 2008, hotels in Gambia were openly advertised in several European countries as malaria-free destinations. During the comparatively short time period of two and a half months between September and November 2008, TropNetEurop member sites reported 56 travellers returning from Gambia with falciparum malaria. Thirty-two of them were male and 24 female. The age range was 15 to 71 years. While the reasons for travel were quite diverse, a striking lack of effective prophylactic measures was apparent in all. Forty-five travellers had not used any malaria chemoprohylaxis. All seven travellers who indicated that they had taken prophylactic drugs used inadequate or those that were absolutely incorrect; two took homeopathic prophylaxis, three used chloroquine only, one used paludrine only, and one stopped taking atovaquone/proguanil too early. Thus, despite the documented risk of complicated infection with falciparum malaria occurring in travellers returning from the Gambia, virtually all travellers chose to use no or inadequate prophylaxis. Information on these cases was published very quickly [38] and consequently the information policies of travel agencies advertising holidays in Ghana were challenged and eventually reversed.

Conclusions

When using all its advantages of clinical vigilance, direct communication and fast feedback, a clinical surveillance network can be remarkably effective in detecting sentinel events and in translating the new information into modifications of clinical practice. Travellers can be very useful when 'serving' as surveillance tools for imported diseases. They travel widely and potentially expose themselves to all types of infectious diseases, they are very mobile, and they return during the incubation period of most diseases to a medical system that is capable of achieving fast and definitive diagnosis. Clustering of infections in returning travellers can be used immediately to warn outbound travellers of a particular risk and to increase their protection. In addition, travellers can also serve as 'canary birds' for disease outbreaks in developing countries that might not be able to provide facilities for rapid diagnosis. Thus, information derived from returning travellers can be invaluable for the host country if channelled back to the medical authorities. TropNetEurop screening for increases in unexpected notifications has proved to be a sensitive early warning tool for the detection of increased transmission rates in endemic countries.

In the future, it is hoped that traditional surveillance systems and recently introduced networks will be able to cooperate more fully. All systems have strengths and weaknesses and can gain from information provided by each other. Thus, linkage of existing networks that would avoid duplication of work and fully exploit the information potential of all combined systems should be encouraged.

References

1. PubMed (2009) http://www.ncbi.nlm.nih.gov/entrez/ (accessed 29 November 2009).
2. NaTHNac (2009) http://www.nathnac.org/ (accessed 29 November 2009).
3. FluNet (2009) http://gamapserver.who.int/GlobalAtlas/home.asp (accessed 29 November 2009).
4. EWGLI (2009) http://www.ewgli.org/ (accessed 29 November 2009).
5. DoDGeis (2009) http://www.geis.fhp.osd.mil/aboutGEIS.asp (accessed 29 November 2009).
6. Talan D *et al.* (1998) EMERGEncy ID NET: an emergency department-based emerging infections sentinel network. *Ann Emerg Med* **32**: 703–711.
7. Freedmann D *et al.* (1999) GeoSentinel: the global emerging infections sentinel network of the international society of travel medicine. *J Travel Med* **6**: 94–98.
8. TropNetEurop (2009) http://www.tropnet.eu (accessed 29 November 2009).
9. Jelinek T *et al.* (2000) European network on imported infectious disease surveillance (TropNetEurop). *Eur Qual Assur News* **11**: 170–172.
10. Jelinek T *et al.* (2002) Clinical and epidemiological characteristics among travellers and immigrants with imported falciparum malaria in Europe: sentinel surveillance data from TropNetEurop. *Clin Infect Dis* **34**: 572–576.
11. Anonymous (1998) Surveillance of malaria in European Union countries. *Eurosurveillance* **3**: 45–47.
12. Anonymous (1999) *Yearbook of Tourism Statistics: World Tourism Organization*. World Health Organization, Madrid.
13. World Tourism Barometer (2009), http://www.unwto.org/facts/eng/barometer.htm (accessed 19 September 2012).
14. Jelinek T *et al.* (1994) Malaria in non-immune travelers: a synopsis of history, symptoms and treatment in 160 patient. *J Travel Med* **1**: 199–202.
15. Matteelli A *et al.* (1999) Epidemiological features and case management practices of imported malaria in northern Italy 1991–1995. *Trop Med Int Health* **4**: 653–657.
16. Nüesch R *et al.* (2000) Hospital admissions for malaria in Basel, Switzerland: an epidemiological review of 150 cases. *J Travel Med* **7**: 95–97.
17. Anonymous (2003) *International Travel and Health Geneva: World Health Organization*. World Health Organization, Madrid.
18. Mühlberger N *et al.* (2003) Age as a risk factor for severe manifestations of falciparum malaria in non-immune patients – observations from TropNetEurop- and SIMPID-surveillance data. *Clin Infect Dis* **36**: 990–995.

19. Jelinek T *et al.* (2002) Imported dengue fever in Europe: sentinel surveillance data from TropNetEurop. *Clin Infect Dis* **35**: 1047–1052.
20. Anonymous (2001) Dengue – USA (Hawaii), http://www.promedmail.org/20010922.2296 (accessed 29 November 2009). ed: ProMED-mail.
21. Lange WR *et al.* (1992) Dengue fever: a resurgent risk for the international traveler. *Am Fam Physician* **45**: 1161–1168.
22. Melissant CF and Kauffmann RH (1992) Infection with Dengue virus. *Neth J Med* **41**: 272–274.
23. Wittesjo B *et al.* (1993) Dengue fever among Swedish tourists. *Scand J Infect Dis* **25**: 699–704.
24. Chippaux A and Poveda JD (1993) Imported dengue in France (1989–1993). Conditions to be met for assuring an accurate etiological diagnosis. *Bull Soc Pathol Exot* **86**: 402–405.
25. Hasler C *et al.* (1993) Imported dengue fever following a stay in the tropics. *Schweiz Med Wochenschr* **123**: 120–124.
26. Pick N and Potasman I (1995) Dengue fever. *Harefuah* **129:** 30–32.
27. Anonymous (1994) Imported dengue – United States, 1992. *MMWR Morb Mortal Wkly Rep* **43**: 97–99.
28. Anonymous (1992) Imported dengue – United States, 1991. *MMWR Morb Mortal Wkly Rep* **41**: 731–732.
29. Anonymous (1995) Imported dengue – United States, 1993–1994. *MMWR Morb Mortal Wkly Rep* **44**: 353–356.
30. Jelinek T *et al.* (2000) Emergence of Falciparum malaria among European tourists to the Dominican Republic. *Emerg Infect Dis* **6**: 537–538.
31. Anonymous (1997) Malaria in the Americas, 1996. *Epidemiol Bull* **18**: 1–8.
32. Castellanos P (1999) Malaria, imported – Europe ex Dominican Rep.(03): ProMED.
33. Jelinek T *et al.* (2002) Cluster of African trypanosomiasis among travellers to the Serengeti. *Emerg Infect Dis* **8**: 634–635.
34. Ponce de Leon S *et al.* (1996) Trypanosoma brucei rhodesiense infection imported to Mexico from a tourist in Kenya. *Clin Infect Dis* **23**: 847–848.
35. Ripamonti D *et al.* (2002) African sleeping sickness in tourists returning from Tanzania: the first 2 Italian cases from a small outbreak among European travelers. *Clin Infect Dis* **34**: e18–e22.
36. Bisoffi Z *et al.* (2003) Illicit trade in humans and risks of disease spread: recurrent clusters of malaria in Chinese illegal immigrants to Europe through Africa. *Emerg Infect Dis* **9**: 1177–1178.
37. Shen J *et al.* (1988) Surveillance for low-level malaria. *Trans R Soc Trop Med Hyg* **92**: 3–6.
38. Jelinek T *et al.* (2008) European cluster of imported falciparum malaria from Gambia. *Eurosurveillance* **13**(51).

Chapter 7 Virus infections in travellers

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Viral hepatitis

Introduction and definitions

The past few decades have witnessed an explosion in knowledge about viral hepatitis, a major public health problem throughout the world affecting several hundreds of millions of people. Viral hepatitis is an important cause of morbidity and mortality, both from acute infection and chronic sequelae, which include, with hepatitis B, hepatitis C and hepatitis D (delta) infection, chronic active hepatitis and cirrhosis, and primary liver cancer with hepatitis B and hepatitis C. The five recognised hepatitis viruses include a range of unrelated human pathogens.

Hepatitis A virus (HAV) is a small, unenveloped, symmetrical RNA virus, which shares many of the characteristics of the family *Picornaviridae*. It is the cause of infectious or epidemic hepatitis transmitted by the faecal–oral route. The virus is classified within the genus Hepatovirus.

Hepatitis B virus (HBV) is a large, double-shelled virus of the hepadnavirus group of double-stranded DNA viruses, which replicate by reverse transcription. The virus is endemic in the human population and hyperendemic in many parts of the world; it is estimated to have infected a third of the world's population. It is transmitted by blood-to-blood contact and by the sexual route.

Hepatitis C virus (HCV) is an enveloped, single-stranded RNA virus, distantly related to flaviviruses, but not transmitted by arthropod vectors. Seroprevalence studies confirm its wide dissemination in all parts of the world and the importance of the parenteral route of transmission, and transmission by blood and blood products, but in as many as 50% of patients the origin of the infection remains unknown. Several genotypes have been described. Infection is common; it is associated with chronic liver disease and with primary liver cancer.

Hepatitis delta virus (*D*) (HDV) is an unusual single-stranded circular RNA virus resembling plant viral satellites and viroids. This virus requires hepadnavirus helper functions for propagation in hepatocytes, and is an important cause of acute and severe chronic liver damage in some regions of the world. The modes of transmission are similar to the parenteral transmission of HBV.

Hepatitis E virus (HEV) is an enterically transmitted, non-enveloped, single-stranded RNA virus, which shares many biophysical and biochemical features with caliciviruses. It has caused large epidemics of acute hepatitis in the Indian subcontinent, Central and Southeast Asia, the Middle East, parts of Africa and elsewhere; it is responsible for high mortality during the third trimester of pregnancy. The number of infections with this virus, particularly in developed countries, may be underestimated.

GB viruses and *hepatitis G virus*. In 1995 two independent viruses, GBV-A and GBV-B, were identified in infectious plasma of tamarin monkeys inoculated with serum from a surgeon (GB) with jaundice. A third virus, GBV-C, was later isolated from a human specimen that was immunoreactive with a GBV-B protein. GBV-C RNA was found in several patients with clinical hepatitis. GBV-A/C, GBV-B and the hepatitis C viruses are members of distinct viral groups whose genomes show regions of sequence identity with flaviviruses. A virus described in 1996 as hepatitis G virus (HGV) is an independent isolate of GBV-C. These viruses do not cause hepatitis in man.

TT virus. TT virus stands for the initials of a patient in Japan with post-transfusion hepatitis. TT virus DNA has been detected in up to 97% of the healthy population in some countries. Preliminary evidence indicates that this virus is similar to members of the family *Circoviridae*, viruses that infect plants and farm animals. The pathogenic role, if any, of this virus in human disease remains to be established. TTV-like mini virus, and several related viruses have been described, but without any disease

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associations in humans. These should not be considered as hepatitis viruses.

Hepatitis A

Introduction and definitions

Epidemics of jaundice have been reported for many centuries and the term 'infectious hepatitis' was coined in 1912 to describe these outbreaks. The term 'hepatitis type A' was adopted by the World Health Organization (WHO) in 1973 to describe this form of hepatitis, and the virus was visualised by electron microscopy in human faecal extracts in the same year. Hepatitis A virus (HAV) is spread by the faecal–oral route. It remains endemic throughout the world and is hyperendemic in areas with poor standards of sanitation and hygiene. Since the end of World War II in 1945, the seroprevalence of antibodies to HAV has declined in many countries. Infection results most commonly from person-to-person contact, but large epidemics do occur. For example, in 1988, an outbreak of hepatitis A associated with the consumption of raw clams in Shanghai resulted in almost 300,000 cases.

Nature of the virus

In 1983, HAV was classified in the genus *Enterovirus* of the family *Picornaviridae*, on the basis of its biophysical and biochemical characteristics, including the stability at low pH. This pre-empted the isolation and analysis of complementary DNA clones that led to the determination of the entire nucleotide sequence of the viral genome. There is limited sequence homology with the enteroviruses and rhinoviruses, although the structure and genome organisation are typical of the picornaviruses. The virus is now classified in the genus *Hepatovirus*. There is only one human serotype of HAV and seven genotypes, but all human HAVs have a single immunodominant epitope, which is responsible for generating neutralising antibodies.

Epidemiology and geographical distribution

Hepatitis A occurs endemically in all parts of the world, with frequent reports of minor and major outbreaks. The exact incidence is difficult to estimate because of the high proportion of subclinical infections and infections without jaundice, differences in surveillance and differing patterns of disease. The degree of under-reporting is very high.

HAV enters the body by ingestion. The virus then spreads, probably by the bloodstream, to the liver, a target organ, where it replicates in the hepatocytes. Large numbers of virus particles are detectable in faeces during the incubation period (Figure 7.1), beginning as early as 10–14 days after exposure and continuing, in general, until peak elevation of serum aminotransferases. Virus is also detected in faeces early in the acute phase of illness, but relatively infrequently after the onset of clinical jaundice. IgG antibody to HAV that

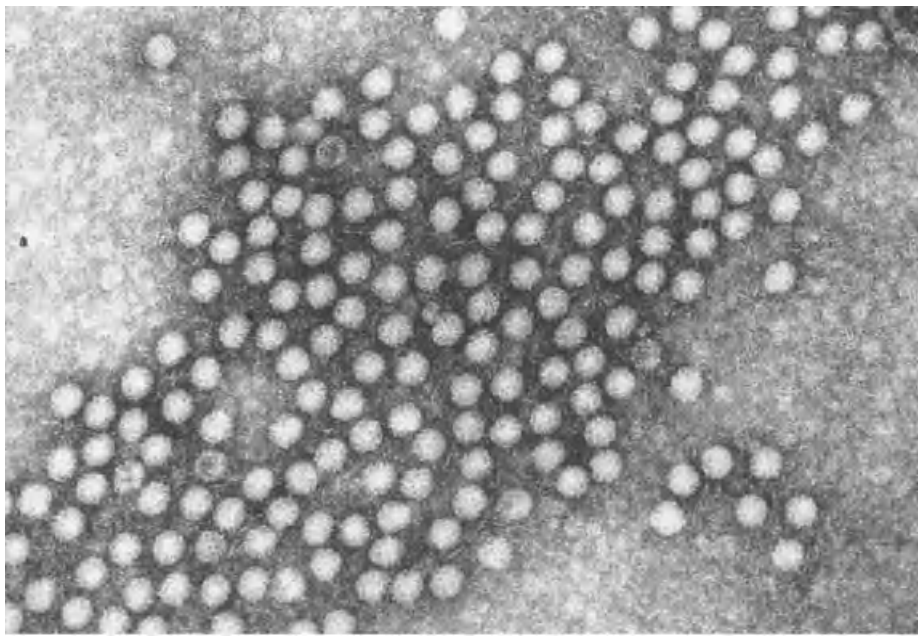

Figure 7.1 Hepatitis A virus: faecal extract from a patient during the incubation period, showing the large number of viral particles (×200,000).

persists is also detectable late in the incubation period, coinciding approximately with the onset of biochemical evidence of liver damage. The virus does not persist and chronic excretion of HAV does not occur. There is no evidence of progression to chronic liver disease.

The mode of transmission of HAV is by the faecal–oral route, most commonly by person-to-person contact in developed countries, and infection occurs readily under conditions of poor sanitation and hygiene, and overcrowding. Common source outbreaks are most frequently initiated by faecal contamination of water and food, but waterborne transmission is not a major factor in maintaining this infection in industrialised communities. On the other hand, many foodborne outbreaks have been reported. This can be attributed to the shedding of large quantities of virus in the faeces during the incubation period of the illness in infected food handlers; the source of the outbreak can often be traced to uncooked food or food that has been handled after cooking. Oysters, clams and other shellfish from contaminated water pose a high risk of infection unless heated or steamed thoroughly. There is a similar risk with uncooked vegetables and crops in countries where raw sewage is used as a fertiliser. Although hepatitis A remains endemic and common in the developed countries, the infection occurs mainly in small clusters, often with only a few identified cases.

Hepatitis A is recognised as an important travel-related infection in travellers from low-prevalence areas to endemic countries. As a generalisation, low-prevalence areas include western Europe, the US and Canada, Australia, New Zealand and Japan. The infection is much more prevalent in other areas of the world, and people travelling to developing countries, including many holiday destinations, are at risk of infection, and are at particularly high risk of infection in rural areas.

Two other sectors of the population are at an increased risk of infection with HAV: those engaging in oral–anal sexual practices and male homosexuality, and injecting drug users. The latter group is at risk because of a combination of poor personal hygiene, faecal contamination of injection equipment, which is often shared, the use of water drawn from toilet pans to dissolve drugs, and possible contamination of illicit drugs that are transported in the intestine after swallowing or are carried in the rectum.

Hepatitis A is rarely transmitted by blood transfusion, although transmission by inadequately inactivated and treated blood coagulation products has been reported, as have cases in patients with cancer treated with lymphokine-activated killer cells and interleukin 2 prepared with tissue culture medium supplemented with pooled human serum.

The incubation period of hepatitis A is 3–5 weeks, with a mean of 28 days. Subclinical and anicteric cases are common and, although the disease has in general a low mortality rate, patients may be incapacitated for many weeks. There is no evidence of progression to chronic liver damage.

Reservoir of infection

The reservoir of HAV is human beings. Rarely, hepatitis A may be transmitted to handlers of chimpanzees and other higher non-human primates. The source of the infection is usually human.

Pathology

Pathological changes are confined to the liver: marked focal activation of sinusoidal lining cells; accumulations of lymphocytes, and especially histiocytes, in the parenchyma, often replacing hepatocytes lost by cytolytic necrosis, predominantly in the periportal areas; occasional coagulative necrosis resulting in the formation of acidophilic bodies and focal degeneration. There are no chronic sequelae.

Clinical features

Inapparent or subclinical infections and infection without jaundice are common with all the different hepatitis viruses, particularly in children under the age of 6 years. The clinical picture ranges from an asymptomatic infection to a mild anicteric illness, to acute disease with jaundice, to severe prolonged jaundice, to fulminant hepatitis.

Differences between the clinical syndromes of acute hepatitis A, acute hepatitis B and other types of viral hepatitis become apparent on analysis of large numbers of well-documented cases, but these differences are not reliable for the diagnosis of individual patients with jaundice.

The following description of the acute illness applies to all types of viral hepatitis. Prodromal non-specific symptoms, such as fever, chills, headache, fatigue, malaise and aches and pains, are followed a few days later by anorexia, nausea, vomiting and right upper quadrant abdominal pain, followed by the passage of dark urine and clay-coloured stools. Jaundice of the sclera and the skin develop. With the appearance of jaundice, there is usually a rapid subjective improvement of symptoms. The jaundice usually deepens for a few days and persists for 1–2 weeks. The faeces then darken and the jaundice diminishes over a period of about 2 weeks. Convalescence may be prolonged.

In areas of high prevalence, most children are infected with hepatitis A early in life and such infections are generally asymptomatic. Infections acquired later in life are of increasing clinical severity. Less than 10% of cases of acute hepatitis A in children up to the age of 6 are icteric, but this increases to 40–50% in the 6–14 age group and to 70–80% in adults.

Of 115,551 cases of hepatitis A in the US between 1983 and 1987, only 9% of the cases, but more than 70% of the fatalities, were in those aged over 49.

Hepatitis A does not persist in the liver, chronic infection does not occur and there is no evidence of progression to chronic liver disease.

Diagnosis

Diagnosis is based on the detection of specific IgM antibodies by serological tests, usually by enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay. Specific IgA antibody responses may also be measured. Specialised laboratories have developed sensitive immunoassays for detection of hepatitis A antigen in faecal samples, and molecular hybridisation can be employed for detection of HAV RNA in faeces. RNA probes have been used for detection of virus in shellfish and in contaminated water.

Management and treatment

Since faecal shedding of the virus is at its highest during the late incubation period and prodromal phase of the illness, strict isolation of cases is not a useful control measure. Spread of hepatitis A is reduced by simple hygienic measures and the sanitary disposal of excreta.

There is no specific treatment for hepatitis A beyond general supportive measures.

Statutory notification to local health authorities is required in a number of countries.

Passive immunisation with normal human immunoglobulin, or in selected circumstances active immunisation with hepatitis A vaccine, is indicated as soon as possible after exposure and within 2 weeks to all household and sexual contacts, and for those exposed to contaminated food. Immunoglobulin should be given to all classroom contacts in day care centres (children under 5 years old), and if there are infants in nappies immunoglobulin should be given to all potentially exposed children and staff in the centre. Immunoglobulin has been used effectively for controlling outbreaks such as in homes for the mentally handicapped. It is not indicated for contacts in the usual office or factory environment or in schools. Hepatitis A vaccine has, however, been shown to be effective for the control of hepatitis A outbreaks in schools.

Protective measures and prevention

General

Strict personal hygiene and good sanitation, with emphasis on thorough handwashing, and sanitary disposal of faeces and urine. Safe and chlorinated water supply. Proper disposal of sewage. Avoid the consumption of raw and inadequately cooked food, including shellfish, in endemic areas.

Passive immunisation

Normal human immunoglobulin, containing at least 100 international units (IU)/ml of anti-HAV antibody, given intramuscularly before exposure to the virus or early during the incubation period will prevent or attenuate a clinical illness. The dosage should be at least 2 IU of anti-HAV antibody per kg body weight, but in special cases, such as pregnancy or in patients with liver disease, that dosage may be doubled.

Immunoglobulin does not always prevent infection and excretion of HAV, and inapparent or subclinical hepatitis may develop. The efficacy of passive immunisation is based on the presence of HAV antibody in the immunoglobulin and the minimum titre of antibody required for protection is believed to be about 10 IU/l.

Immunoglobulin is used most commonly for close personal contacts of patients with hepatitis A and for those exposed to contaminated food. It has also been used effectively for controlling outbreaks in institutions such as homes for the mentally handicapped and in nursery schools. Prophylaxis with immunoglobulin is recommended for persons without HAV antibody visiting highly endemic areas. After a period of 6 months the administration of immunoglobulin for travellers needs to be repeated, unless it has been demonstrated that the recipient has developed HAV antibodies. Active immunisation for travellers is therefore preferred and is strongly recommended.

Active immunisation

Killed hepatitis A vaccines are prepared from virus grown in tissue culture and inactivated with formalin. The first such vaccine was licensed in 1992 and several preparations are available, including a combined hepatitis A and B vaccine. These vaccines are highly immunogenic and provide long-term protection against infection. Several such vaccines are available, including combined vaccines with hepatitis B vaccine and with typhoid vaccine.

In areas of high prevalence, most children have antibodies to HAV by the age of 3 years and such infections are generally asymptomatic. Infections acquired later in life are of increasing clinical severity. It is important, therefore, to protect those at risk because of personal contact or because of travel to highly endemic areas. Other groups at risk of hepatitis A infection include staff and residents of institutions for the mentally handicapped, day care centres for children, sexually active male homosexuals, intravenous narcotic drug abusers,

food handlers, sewage workers, healthcare workers, military personnel and members of certain low socioeconomic groups in defined community settings. Patients with blood coagulation defects and patients with chronic liver disease should be immunised against hepatitis A.

In some developing countries the incidence of clinical hepatitis A is increasing as improvements in socioeconomic conditions result in infection later in life; protection by immunisation would be prudent but strategies are yet to be agreed. Global control of hepatitis A will require universal immunisation of infants and will become possible when HAV vaccine is combined in a polyvalent form with other childhood vaccines such as diphtheria, pertussis, tetanus, measles, rubella, mumps and hepatitis B.

Hepatitis B

Introduction and definitions

Hepatitis B was referred to originally as 'serum hepatitis'; it is the most common form of parenterally transmitted viral hepatitis, and an important cause of acute and chronic infection of the liver in many countries. More than a third of the world's population had been infected with hepatitis B virus (HBV), and WHO estimates that it results in 1–2 million deaths every year.

The clinical features of acute infection resemble those of the other viral hepatitides. The virus persists in approximately 5–10% of immunocompetent adults, and in as many as 90% of infants infected perinatally. Persistent carriage of hepatitis B, defined by the presence of hepatitis B surface antigen (HBsAg) in the serum for more than 6 months, has been estimated to affect about 350 million people worldwide, although not all carriers are infectious. Long-term continuing virus replication may lead to progression to chronic liver disease, cirrhosis and hepatocellular carcinoma. Primary liver cancer is one of the 10 most common cancers worldwide and 80% of such cancers are ascribed to persistent infection with HBV.

Nature of the virus

The hepatitis B virion is a 42 nm particle comprising an electron-dense nucleocapsid or core (HBsAg) 27 nm in diameter, surrounded by an outer envelope of the surface protein (HBsAg) embedded in membraneous lipid derived from the host cell (Figure 7.2). The surface antigen, originally referred to as Australia antigen, is produced in excess by the infected hepatocytes and is secreted in the form of 22 nm particles and tubular structures of the same diameter.

The nucleocapsid of the virion consists of the viral genome surrounded by the core antigen. The genome, which is

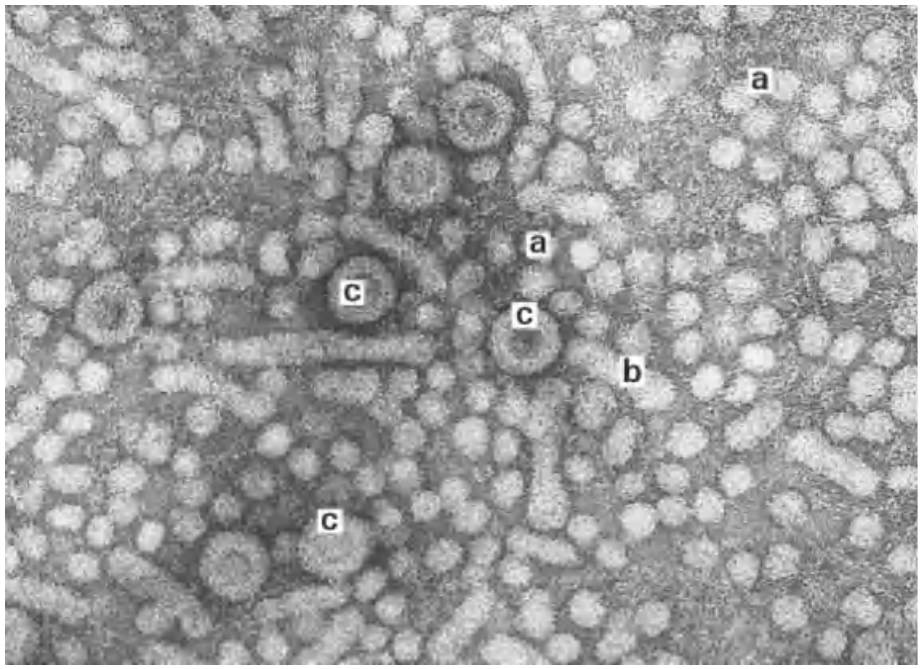

Figure 7.2 Hepatitis B virus: (a) small spherical particles representing excess viral coat protein; (b) tubular structures; (c) double-shelled complete virus (×400,000).

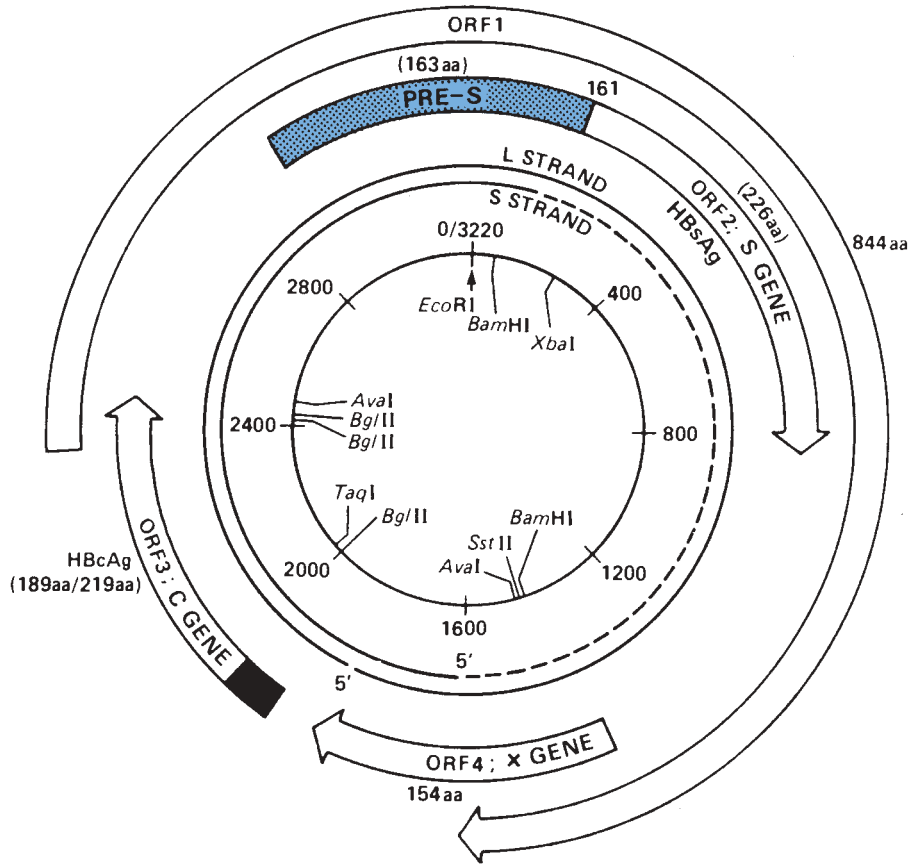

Figure 7.3 The molecular structure of the genome of hepatitis B virus.

approximately 3.2 kilobases in length, has an unusual structure and is composed of two linear strands of DNA held in a circular configuration by base-pairing at the 5′ ends. One of the strands is incomplete and the 3′ end is associated with a DNA polymerase, which is able to complete that strand in the presence of deoxynucleoside triphosphates (Figure 7.3).

The genomes of many isolates of HBV have been cloned and the complete nucleotide sequences determined. Analysis of the coding potential of the genome reveals four open reading frames (ORFs), which are conserved between all of these isolates, but there is some variation in sequence of up to 12% of nucleotides. The first ORF encodes the various forms of the surface protein. The core ORF has two in-phase initiation codons. The 'precore' region is highly conserved, has the properties of a signal sequence and is responsible for the secretion of HBeAg. The third ORF, which is the largest and overlaps the other three, encodes the viral polymerase. The fourth ORF was designated 'x' because the function of its small gene product was not known initially; however, 'x' has now been demonstrated to be a transcriptional transactivator, and may enhance the expression of other viral proteins.

Surface antigen epitopes

There is a variation in the epitopes presented on the surface of the virions and subviral 22 nm particles so that there are several subtypes of HBV, which differ in their geographical distribution. All isolates of the virus share a common epitope, *a*, a domain of the major surface protein which is believed to protrude as a double loop from the surface of the particle. Two other pairs of mutually exclusive antigenic determinants, *d* or *y*, and *w* or *r*, are also present on the major surface protein. These variations have been correlated with single nucleotide changes in the surface ORF, which led to variation in single amino acids in the protein. Four principal subtypes of HBV are recognised: *adw*, *adr*, *ayw* and *ayr*. Subtype *adw* predominates in northern Europe, the Americas and Australasia, and also is found in Africa and Asia. Subtype *ayw* is found in the Mediterranean region, eastern Europe, northern and western Africa, the Near East and the Indian

subcontinent. In the Far East, *adr* predominates but the rarer *ayr* may occasionally be found in Japan and Papua New Guinea. Other less common variants exist as a result of subdivision of the principal antigenic determinants. More recently, subtyping has been carried out by DNA sequencing of the surface antigen gene, and at least six genotypes, A–F, which differ by more than 8% in the protein sequence, have been identified. Subtyping is mainly of epidemiological or phylogenetic significance.

Surface antigen mutants

Production of antibodies to the group antigenic determinant *a* mediates cross-protection against all subtypes, as has been demonstrated by challenge with a second subtype of the virus following recovery from an initial experimental infection. The epitope a is located in the region of amino acids 124–148 of the major surface protein, and appears to have a double-loop conformation. A monoclonal antibody that recognises a region within this a epitope is capable of neutralising the infectivity of HBV for chimpanzees, and competitive inhibition assays using the same monoclonal antibody demonstrate that equivalent antibodies are present in the sera of subjects immunised with either plasma-derived or recombinant hepatitis B vaccine.

During a study of the immunogenicity and efficacy of hepatitis B vaccines in Italy, a number of individuals who had apparently mounted a successful immune response and became anti-surface antibody (anti-HBs) positive, later became infected with HBV. These cases were characterised by the coexistence of non-complexed anti-HBs and HBsAg, and there were other markers of hepatitis B infection. Further examination of the antigen using monoclonal antibodies suggested that the a epitope was either absent or masked by antibody. Subsequent sequence analysis of the virus from one of these cases revealed a mutation in the nucleotide sequence encoding the a epitope, the consequence of which was a substitution of arginine for glycine at amino acid position 145. There is now considerable evidence for a wide geographical distribution of the point mutation in the genome of HBV from guanosine to adenosine at position 587, resulting in an amino acid substitution at position 145 from glycine to arginine in the highly antigenic group determinant a of the surface antigen. This is a stable mutation that has been found in viral isolates from children and adults and it has been described in Italy, Singapore, Japan, Brunei, Taiwan, India, US and elsewhere, and from liver transplant recipients with hepatitis B in the US, Germany and the UK who had been treated with specific hepatitis B immunoglobulin or humanised hepatitis B monoclonal antibody, and in patients with chronic hepatitis in Japan and elsewhere. Other point mutations and substitutions have also been described. The 145 mutation appears to be the most common and to be stable. The region in which this mutation occurs is an important virus epitope to which vaccine-induced neutralising antibody binds, as discussed above, and the mutant virus is not neutralised by antibody to this specificity. The 145 variant virus can replicate as a competent virus, implying that the amino acid substitution does not alter the attachment of the virus to the liver cell. Variants of HBV with altered antigenicity of the envelope protein show that HBV is not as antigenically singular as believed previously and that humoral escape mutation can occur *in vivo*. This finding gives rise to two causes for concern: failure to detect HBsAg may lead to transmission through donated blood or organs, and HBV may infect individuals who are anti-HBs positive after immunisation.

Mathematical modelling suggests that HBV variants may become dominant over the current wild-type virus in 50–100 years.

HBV precore mutants

In 1988, a report was published on the nucleotide sequence of the genome of a strain of HBV cloned from the serum of a naturally infected chimpanzee. A surprising feature was a point mutation in the penultimate codon of the precore region to a termination codon. This mutation was found subsequently in some patients with anti-HBe who were positive for HBV DNA in serum by hybridisation. In most cases there was an additional mutation in the preceding codon. Precore variants have been described in many patients with severe chronic liver disease and some failed to respond to treatment with interferon. It has been suggested that the mutants are more pathogenic than the wild-type virus. A precore variant that produces hepatitis B e antigen has also been described.

Replication of HBV

HBV and the animal hepadnaviruses are unique among animal DNA viruses in that they replicate through an RNA intermediate.

Epidemiology and geographical distribution

Although various body fluids (blood, saliva, menstrual and vaginal discharges, serous exudates, seminal fluid and breast milk) have been implicated in the spread of infection, infectivity appears to be especially related to blood and to body fluids contaminated with blood. The epidemiological propensities of this infection are therefore wide; they include infection by inadequately sterilised syringes and

instruments, transmission by unscreened blood transfusion and blood products, by close contact, and by both heterosexual and homosexual contact. Antenatal (rarely) and perinatal (frequently) transmission of hepatitis B infection from mother to child may take place; in some parts of the world (Southeast Asia), perinatal transmission is very common.

It should be noted that transmission of the infection may result from accidental inoculation of minute amounts of blood or fluid contaminated with blood during medical, surgical and dental procedures; immunisation with inadequately sterilised syringes and needles; intravenous and percutaneous drug abuse; tattooing; ear, nose and body piercing; acupuncture; laboratory accidents; and accidental inoculation with razors and similar objects that have been contaminated with blood. Additional factors may be important for the transmission of hepatitis B infection in the tropics; these include traditional tattooing and scarification, blood letting, ritual circumcision and repeated biting by blood-sucking arthropod vectors. Investigation of the role that biting insects may play in the spread of hepatitis B has yielded conflicting results. HBsAg has been detected in several species of mosquitoes and in bed bugs that were either trapped in the wild or fed experimentally on infected blood, but no convincing evidence of replication of the virus in insects has been obtained. Mechanical transmission of the infection, however, is a possibility, but does not appear to be an important route of transmission of HBV.

The incubation period of hepatitis B is 2–6 months. HBsAg first appears during the late stages of the incubation period, 2–8 weeks before the appearance of abnormal liver function tests and jaundice, and is easily detectable by radioimmunoassay or enzyme immunoassay. Enzyme immunoassay is specific and highly sensitive and is used widely in preference to radioisotope methods. The antigen persists during the acute phase of the disease and sharply decreases when antibody to the surface antigen becomes detectable. Antibody of the IgM class to the core antigen is found in the serum after the onset of the clinical symptoms and slowly declines after recovery. Its persistence at high titre suggests continuation of the infection. Core antibody of the IgG class persists for many years and provides evidence of past infection.

During the incubation period and during the acute phase of the illness, surface antigen–antibody complexes may be found in the sera of some patients. Immune complexes have been found by electron microscopy in the sera of all patients with fulminant hepatitis, but are seen only infrequently in non-fulminant infection. Immune complexes also are important in the pathogenesis of other disease syndromes characterised by severe damage of blood vessels, for example polyarteritis nodosa, some forms of chronic glomerulonephritis and infantile papular acrodermatitis.

The distribution of infection with HBV varies between geographical regions but it is endemic in all countries and hyperendemic in many parts of the world. Survival of the virus is ensured by the huge reservoir of carriers, estimated conservatively to number in excess of 350 million worldwide, of whom more than 75% are from Southeast Asia and the Western Pacific Region. Other hyperendemic regions include many countries in sub-Saharan Africa. Based on the prevalence of HBsAg among blood donors, a highly selected group, prevalence rates in 1970–1980 extrapolated to the general population were as follows:

- 0.1% or less in northern Europe, North America and Australasia
- up to 5% in southern Europe, the countries bordering the Mediterranean and parts of Central and South America
- 10–20% or more in some parts of Africa, Southeast Asia and the western Pacific.

Reservoir of infection

The human population. The animal hepadnaviruses do not infect humans and they all have a narrow host range.

Pathology

Pathological changes in the liver include: conspicuous focal activation of sinusoidal cells; accumulation of lymphocytes and histiocytes in the parenchyma, often replacing hepatocytes lost by cytolytic necrosis, mainly in the periportal areas; focal degeneration; and occasional coagulative necrosis. It has been reported that acute hepatitis B is characterised by more extensive parenchymal abnormalities and inflammatory changes than those found in hepatitis A, whereas portal inflammation and cholestasis are less prominent.

Immune responses

Antibody and cell-mediated immune responses to various types of antigens are induced during acute infection; however, not all these are protective and, in some instances, may cause autoimmune phenomena that contribute to disease pathogenesis. The immune response to infection with HBV is directed towards at least three antigens: HBsAg, the core antigen and the e antigen. The view that hepatitis B exerts its damaging effect on hepatocytes by direct cytopathic changes is inconsistent with the persistence of large quantities of the surface antigen in liver cells of many apparently healthy carriers. Additional evidence suggests that the pathogenesis of liver damage in the course of hepatitis B infection is related to the immune response by the host.

Clinical features and diagnosis

The clinical features of acute hepatitis B are similar to those of acute hepatitis A and the other hepatitides. Direct demonstration of virus in serum samples is feasible by visualising the virus particles by electron microscopy, by detecting virus-associated DNA polymerase, and by assay of viral DNA and its amplification by various techniques. All these direct techniques are often impractical in the general diagnostic laboratory, and specific diagnosis must therefore rely on serological tests. Many serological tests, mainly based on ELISA and less commonly used radioimmunoassays, are available for markers of infection with HBV. HBsAg first appears during the late stages of the incubation period and persists during the acute phase, declining rapidly when antibody to the surface antigen (anti-HBs) becomes detectable. Antibody of the IgM class to the core antigen is found in the serum after the onset of clinical symptoms; it slowly declines after recovery and is replaced by IgG anticore, which persists for many years. Hepatitis B e antigen appears during the acute phase of illness and anti-e is detectable with recovery. Molecular techniques are available for HBV DNA polymerase and HBV DNA.

Management and treatment

There is no specific treatment for acute hepatitis B, but significant developments have been reported with antiviral therapy of chronic infection with interferon alpha and combination therapy with several nucleoside analogues. The various nucleoside analogues used for the treatment of chronic hepatitis B inhibit different phases of replication of the virus.

Prevention of hepatitis B

General measures are based on knowledge of the mode of transmission of hepatitis B and include measures to prevent blood-to-blood contact; the use of sterile syringes, needles and other implements; screening of blood and blood products; protected casual sexual intercourse; and other precautions dictated by the propensity for spread of this infection and the huge number of asymptomatic carriers of HBV in the population. The single most effective measure for prevention is active immunisation.

Passive immunisation with immunoglobulin

Hepatitis B immunoglobulin is prepared specifically from pooled plasma with high titre of hepatitis B surface antibody and may confer temporary passive immunity under certain defined conditions. The major indication for the administration of hepatitis B immunoglobulin is a single acute exposure to HBV, such as occurs when blood containing surface antigen is inoculated, ingested or splashed on to mucous membranes and the conjunctiva. It should be administered as early as possible after exposure and preferably within 48 h, usually 3 ml (containing 200 IU/ml anti-HBs) in adults. It should not be administered 7 days or more after exposure. It is generally recommended that two doses of hepatitis B immunoglobulin should be given 30 days apart.

Results with the use of hepatitis B immunoglobulin for prophylaxis in neonates at risk of infection with HBV are good if the immunoglobulin is given as soon as possible after birth or within 12 h of birth. Combined passive and active immunisation indicate an efficacy approaching 90%.

Active immunisation

The major humoral antibody response of recipients of hepatitis B vaccine is to the common *a* epitope, with consequent protection against all subtypes of the virus. First-generation inactivated vaccines were prepared from 22 nm H-BsAg particles purified from plasma donations from chronic carriers. These preparations are safe and immunogenic but have been superseded in some countries by recombinant vaccines produced by the expression of HBsAg in yeast cells. The expression plasmid contains only the 3′ portion of the HBV surface ORF and only the major surface protein, without pre-S epitopes, is produced. Vaccines containing pre-S2 and pre-S1 as well as the major surface proteins expressed by recombinant DNA technology are undergoing clinical trial.

In many areas of the world with a high prevalence of HBsAg carriage, such as China and Southeast Asia, the predominant route of transmission is perinatal. Although HBV does not usually cross the placenta, the infants of viraemic mothers have a very high risk of infection at the time of birth, and immunisation protects the infant against perinatal infection.

Immunisation against hepatitis B is now recognised as a high priority in preventive medicine in all countries and strategies for immunisation are being revised. Universal vaccination of infants and adolescents is under examination as the strategy to control the transmission of this infection. More than 160 countries now offer hepatitis B vaccine to all children, including the US, Canada, Italy, France and most western European countries. However, immunisation against hepatitis B is at present recommended in a number of countries with a low prevalence of hepatitis B only to groups that are at an increased risk of acquiring this infection. These groups include:

- individuals requiring repeated transfusions of blood or blood products

- individuals requiring prolonged inpatient treatment
- patients who require frequent tissue penetration or need repeated circulatory access
- patients with natural or acquired immune deficiency
- patients with malignant diseases.

Viral hepatitis is an occupational hazard among healthcare personnel and the staff of institutions for the mentally handicapped, and in some semi-closed institutions. High rates of infection with hepatitis B occur in narcotic drug addicts and intravenous drug abusers, sexually active male homosexuals and prostitutes. Individuals working in areas of high endemicity are also at an increased risk of infections. Women in areas of the world where the carrier state in the group is high are another segment of the population requiring immunisation, in view of the increased risk of transmission of the infection to their offspring. Young infants, children and susceptible persons living in certain tropical and subtropical areas where present socioeconomic conditions are poor and the prevalence of hepatitis B is high should also be immunised.

Hepatitis B and the traveller

The risk of hepatitis A and hepatitis B to the traveller should not be underestimated. Travellers must take commonsense precautions to reduce the risk of hepatitis B, as outlined above. Great caution is required in any casual intimate or sexual contact, particularly with prostitutes and male homosexuals. All procedures involving penetration of the skin or mucous surfaces must be avoided if possible, including any injections, tattooing, ear and other body piercing, blood transfusion and medical and dental procedures carried out under questionable hygienic conditions.

Immunisation against hepatitis A and hepatitis B is strongly recommended for all travellers to hyperendemic areas, and it is a sensible precaution in case of accidents that require treatment. Combined hepatitis A and B vaccines are available, are highly effective and are strongly recommended for all travellers.

Hepatitis D

Introduction and definitions

Delta hepatitis was first recognised following the detection of a novel protein, termed delta antigen, by immunofluorescent staining in the nuclei of liver cells in biopsy specimens from patients with chronic active hepatitis B. Later this antigen was found to be a component of a new RNA virus enveloped by the surface antigen of HBV. Hepatitis delta virus (HDV) requires a helper function of HBV for its transmission.

Two forms of delta hepatitis infection are known. In the first, a susceptible individual is co-infected with HBV and HDV, often leading to a more severe form of acute hepatitis caused by HBV. In the second, an individual infected chronically with HBV becomes superinfected with HDV. This may cause a second episode of clinical hepatitis and accelerate the course of the chronic liver disease, or cause overt disease in asymptomatic carriers of hepatitis B. HDV is cytopathic and HDAg may be directly cytotoxic.

Delta hepatitis is common in the Mediterranean region, parts of eastern Europe, the Middle East, Africa, South America and some islands in the South Pacific region. It has been estimated that 5% of hepatitis B carriers worldwide (approximately 18 million people) are infected with HDV. In areas of low prevalence of HBV, those at high risk of hepatitis B, particularly intravenous drug abusers, are also at risk of HDV infection.

Nature of the infectious agent

HDV is approximately 36 nm in diameter, with an RNA genome associated with delta antigen (HDAg) surrounded by an outer lipoprotein coat of HBV, HBsAg. The genome is a closed circular RNA molecule of between 1,670 and 1,685 nucleotides, with some genetic heterogeneity, and resembles those of the satellite viroids and virusoids of plants. Unlike the plant viroids, HDV codes for delta antigen. This is encoded by an ORF in the antigenomic RNA but four other ORFs that are also present in the genome do not appear to be used.

There appear to be three genotypes. Genotype I is the commonest and isolates have been obtained from all parts of the world. Genotype II represent isolates in Taiwan, and this genotype appears to be associated with less severe disease. Genotype III from South America is associated with a fulminant form of hepatitis.

HDV replicates only in hepatocytes and most probably uses the same cell receptors as HBV. Once inside the cells, HDV can replicate in the nuclei in the absence of HBV.

Epidemiology and geographical distribution

HDV is bloodborne and is transmitted in the same manner as HBV, essentially by the parenteral route by blood-to-blood contact. The virus is also spread by the sexual route, although less readily than HBV, at a rate of about 10%.

Infection with delta hepatitis has been detected among carriers of HBsAg throughout the world and is referred to as superinfection, but the distribution of HDV is uneven. The

infection is endemic in countries bordering the Mediterranean, particularly in southern Italy and in Greece, where as many as 25% of carriers of HBsAg are co-infected. High rates of infection have been found in eastern Europe, particularly in Romania; the former Soviet Union; South America, particularly the Amazon Basin, Venezuela, Columbia (hepatitis de Sierra Nevada de Santa Marta), Brazil (Labrea black fever) and Peru; parts of Africa, particularly West Africa; and some isolated Pacific Islands. In northern Europe, the US and Australia, HDV infection is relatively uncommon, except among high-risk groups such as intravenous drug abusers and multiply transfused patients such as patients with haemophilia.

Reservoir of infection

The infection has only been detected in humans.

Pathology

The histological changes are, in general, similar to those of other forms of acute viral hepatitis, with the additional feature of hepatitis delta antigen detected by immunostaining. The histopathological changes in patients with chronic delta hepatitis are those characteristic of chronic hepatitis, except that they tend to be severe.

Clinical features and diagnosis

In general, the clinical features of acute co-infection with HDV and HBV are similar to the other forms of hepatitis but tend to be more severe than infection with HBV alone. The picture is complicated, however, and is more severe in some geographical regions, for example South America, and particularly in the case of superinfection with HDV of carriers of hepatitis B with underlying chronic liver disease and active replication of HBV. There is also an association with the genotypes of HDV. Genotype I is predominant throughout the world. Genotype II, which is predominant in Taiwan and in Japan, appears to be less virulent and is associated less frequently with fulminant hepatitis in the acute stage of the disease and in chronic liver disease. Genotype III has so far only been found in northern South America, where hepatitis delta is endemic and acute infections have been associated with severe hepatitis outbreaks with high mortality.

It should be noted that, while generally patients with hepatitis D tend to suffer from a more serious and more often progressive disease than patients with other forms of viral hepatitis, subclinical infections and self-limited infections are common with co-infections of HDV and HBV, in contrast to superinfections with HDV of chronic carriers of HBV.

Diagnosis of hepatitis delta infection is based on a number of tests, including antibodies to delta antigen (anti-HDV), measurements of anti-HDV of the IgM class, detection of delta antigen in serum by immunoassays and in liver biopsies by immunohistochemistry, and detection of HDV RNA by molecular techniques particularly reverse transcriptase polymerase chain reaction (RT-PCR).

Management and treatment

There is no treatment for acute infection. Interferon is of limited efficacy in chronic hepatitis D but sustained clearance of HBsAg has been reported in a few patients with short duration of hepatitis D. Other antiviral drugs which have been employed for the treatment of chronic hepatitis B have not been successful. Liver transplantation is a treatment option for end-stage chronic delta liver disease.

Prevention

General protective measures are similar to those recommended for hepatitis B and other bloodborne viral diseases. Prevention of hepatitis D can be achieved by immunisation against hepatitis B in those who are susceptible to hepatitis B. Healthy individuals who are immunised effectively against hepatitis B cannot be coinfected with HDV, as HDV requires a helper function of HBV. A specific HDV vaccine will be required for prevention of superinfection of chronic carriers of HBV, and limited experimental evidence in animals indicates that this approach may be feasible.

Hepatitis E

Introduction and definitions

Epidemic hepatitis, which resembles hepatitis A but is caused by a distinct and different virus, has been reported in the Indian subcontinent, Central and Southeast Asia, the Middle East, North and East Africa, and Central America. Outbreaks involving tens of thousands of cases have been reported, and hepatitis E virus (HEV) is also a common cause of sporadic acute hepatitis in these countries. Sporadic cases have been seen in other countries and in the highly developed (industrialised) countries in returning travellers from the areas listed above and among migrant labourers, and also sporadic infections in patients who had not travelled abroad. The infection is acute and self-limiting but it is associated with high mortality (10–40%) in pregnant women during the third trimester of pregnancy.

Nature of the infectious agent

Morphologically the virus is spherical and unenveloped, measuring 32–34 nm in diameter, with spikes and indentations visible on the surface of the particle. The particles contain a single-stranded positive-sense RNA genome. Physicochemical studies have shown that the virus is very labile and sensitive to freeze-thawing, caesium chloride and pelleting by ultracentrifugation. The genome of the virus is a polyadenylated, positive-sense RNA of about 7,200 nucleotides, which contains three ORFs. At least seven different genotypes of HEV exist worldwide, and numerous novel strains have been identified from different regions of the world, including the US, Italy, Greece, Taiwan and China. These novel strains of HEV are distinct from all known strains, such as Burma and Mexico, and from each other. Molecular cloning of the genome of HEV and the expression by recombinant DNA technology of various HEV proteins has led to the development of diagnostic tests, although there are problems of specificity with a number of the assays.

The discovery of a virus in herds of swine in the US and Taiwan that is closely related to HEV is of interest, although it has not yet been established whether this virus can infect humans.

The various properties of HEV suggest that this virus is similar to the caliciviruses, although HEV resembles most closely the sequences of rubella virus and a plant virus, beet necrotic yellow vein virus. However, recent studies indicate that HEV is a single member of a novel virus genus, Hepevirus.

Epidemiology and geographical distribution

HEV is spread predominantly by drinking water that is contaminated with human faecal material. Transmission by contaminated food is also likely. The ingestion of contaminated water in regions where HEV is endemic, e.g. in India, Pakistan, Egypt, Burma, China, parts of Russia and the former Soviet Union, and parts of Africa and Central America, may result in the infection of thousands of people, predominantly young adults. Sporadic cases are also common in these countries and in returning travellers. Improved serological diagnosis in recent years has led to better understanding of the epidemiology of hepatitis E. For example, seroprevalence studies in Hong Kong indicate that hepatitis E accounts for some 30% of all cases of non-A, non-B, non-C hepatitis, and HEV was found to be a common cause of acute hepatitis in children in Egypt. Sporadic cases in industrialised countries in western Europe and North America in persons who had not travelled outside their country nor had been in contact with returning travellers may be the result of zoonotic infection, for example by contact with infected swine, cattle, deer, rats and other animals.

Reservoir of infection

Humans are the principal reservoir of infection. A virus similar to HEV has been detected in herds of swine and other mammalian hosts in a number of countries, but there is only limited evidence of cross-species transmission so far.

Pathology

Histopathological features in the liver are similar to those of other forms of hepatitis, although cholestasis may be more prominent. Ultrastructural changes in the liver after experimental transmission to non-human primates include the finding of 27–34 nm virus particles during the acute phase of the infection. It is not known whether the virus causes cell injury directly or whether the changes in the liver reflect immune-mediated damage.

Clinical features and diagnosis

The average incubation period is a little longer than with hepatitis A, with a mean of 6 weeks. The virus is spread by water and food contaminated by faeces. Secondary cases do not appear to be common. Individual cases cannot be differentiated from other cases of viral hepatitis on the basis of clinical features, although cholestatic features may be more prominent, and fulminant hepatic failure occurs in 10–20% during the third trimester of pregnancy. In epidemics, most clinical cases, which occur predominantly in young adults, will exhibit anorexia, jaundice and hepatomegaly. Serological tests indicate that clinically inapparent cases occur. There is no evidence of persistence of the virus in the liver, nor of prolonged excretion in faeces. Chronic liver disease does not occur.

The expression of viral proteins by recombinant DNA technology has led to the development of many diagnostic and research immunoassays. Techniques based on antigenic components of linear peptide epitopes are also available but there is a lack of concordance between many of the assays, particularly with failure to detect hepatitis E antibodies in convalescent sera, and with heterologous strains of the virus. However, considerable improvement of diagnostic reagents has been reported more recently, using other viral proteins and virus-like particles expressed in baculovirus systems. Detection of HEV RNA in serum and faeces by molecular techniques such as RT-PCR is reliable, but at present limited to reference laboratories.

Management and treatment

There is no specific treatment for hepatitis E infection beyond supportive measures.

Prevention

General protective measures are based on strict hygienic precautions and those outlined for hepatitis A in relation to drinking water and consumption of uncooked food. Passive immunisation with immunoglobulin derived from plasma collected in endemic areas does not offer protection against infection with HEV. This reflects the fact that adult populations in endemic regions, who are very likely to have been exposed to HEV in early life, are susceptible to infection with this virus, with high attack rates during epidemics. Vaccines against HEV are undergoing clinical trials.

Hepatitis C

Introduction and definitions

Specific laboratory diagnosis of hepatitis types A, B and delta revealed an unrecognised form of hepatitis that was clearly unrelated to any of these three types of virus. Surveys of post-transfusion hepatitis after the administration of blood and blood products screened for hepatitis B by highly sensitive techniques provided strong epidemiological evidence of 'guilt by association' of an infection of the liver referred to as non-A, non-B hepatitis.

Attempts to clone the agent of parenterally transmitted non-A, non-B hepatitis were made from a plasma known to contain high titre of the agent by experimental transmission to non-human primates. Because it was not known whether the genome was DNA or RNA, a denaturation step was included before the synthesis of complementary DNA so that either DNA or RNA could serve as a template. The resultant cDNA was then inserted into the bacteriophage expression vector λ gt 11 and the libraries screened using serum from a patient with chronic non-A, non-B hepatitis. This led to the detection of a clone that was found to bind to antibodies present in the sera of patients infected with non-A, non-B hepatitis. This clone was used as a probe to detect a larger, overlapping clone in the same library. These sequences hybridised to a positive-sense RNA molecule of about 10,000 nt, which was present in the livers of infected chimpanzees but not in uninfected controls. Homologous sequences were not detected in the chimpanzee or human genomes. By employing a 'walking' technique, the newly detected overlapping clones were used as hybridisation probes to detect further virus-specific clones in the library. Thus, clones covering the entire viral genome were assembled and the completed nucleotide sequence of hepatitis C virus was determined.

Infection with hepatitis C virus (HCV) is prevalent throughout the world, and persistent infection and chronic liver disease are common.

Nature of the infectious agent

The amino acid sequence of the nucleocapsid protein is highly conserved among different isolates of HCV. The next domain in the polyprotein also has a signal sequence at its C-terminus and may be processed in a similar fashion. The product is a glycoprotein, which is probably found in the viral envelope and is variably termed E1/S. The third domain may be cleaved by a protease within the viral polyprotein to yield what is probably a second surface glycoprotein, E2/NS1. These proteins are of considerable interest because of their potential use for tests for the direct detection of viral proteins and for the development of HCV vaccines. Nucleotide sequencing reveals that both domains contain hypervariable regions.

The non-structural region of the HCV genome is divided into regions NS2 to NS5. In the flaviviruses, NS3 has two functional domains, a protease that is involved in cleavage of the non-structural region of the polyprotein and a helicase that is presumably involved in RNA replication. Motifs within this region of the HCV genome have homology to the appropriate consensus sequences, suggesting similar functions.

The genome of HCV comprises about 10,000 nt of positive-sense RNA, lacks a 3′ poly-A tract and has a similar gene organisation to members of the family *Flaviviridae* and is considered the prototype of the genus *Hepacivirus*. All of these genomes contain a single large ORF, which is translated to yield a polyprotein (of around 3,000 amino acids in the case of HCV) from which the viral proteins are derived by post-translational cleavage and other modifications.

HCV consists of a family of highly related viruses, but nevertheless there are up to 11 distinct genotypes and various subtypes with differing geographical distribution. There is no firm evidence of an association between genotypes and greater pathogenicity. The C, NS3 and NS4 domains are the most highly conserved regions of the genome, and therefore these proteins are the most suitable for use as capture antigens for broadly reactive tests for antibodies to HCV.

The degree of divergence apparent within the viral envelope proteins implies the absence of a broad cross-neutralising antibody response to infection by viruses of different groups. In addition, there is considerable sequence heterogeneity among almost all HCV isolates in the N-terminal region of E2/NS1, suggesting that this region may be under strong

immune selection. Sequence changes within this region may occur during the evolution of disease in individual patients and may play an important role in progression to chronicity.

Epidemiology and geographical distribution

Infection with HCV occurs throughout the world. Much of the seroprevalence data are based on blood donors, who represent a selected population. The prevalence of antibodies to HCV in blood donors varies from 0.02% to 1.25% in different countries. Higher rates have been found in southern Italy, Spain, central Europe, Japan and parts of the Middle East, with as many as 19% in Egyptian blood donors. Until screening of blood donors was introduced, hepatitis C accounted for the vast majority of non-A, non-B post-transfusion hepatitis. However, it is clear that while blood transfusion and the transfusion of blood products are efficient routes of transmission of HCV, these represent a small proportion of cases of acute clinical hepatitis in a number of countries (with the exception of patients with haemophilia).

Current data indicate that in 50% or more of patients in industrialised countries, the source of infection cannot be identified; although transmission by contact with blood and contaminated materials is likely to be important, 35% of patients have a history of intravenous drug misuse. Household contact and sexual exposure do not appear to be major factors in the epidemiology of this common infection, and occupational exposure in the healthcare setting accounts for about 2% of cases. Transmission of HCV from mother to infant occurs in about 10% of viraemic mothers and the risk appears to be related to the level of viraemia. It should be noted, however, that information on the natural history of hepatitis C is limited because the onset of the infection is often unrecognised and the early course of the disease is indolent and protracted in most patients. Co-infection with HBV is not uncommon.

Reservoir of infection

The only known reservoir of infection is humans.

Pathology

There is evidence that 50–80% or more of infections with HCV progress to chronic liver disease. Histological examination of liver biopsies from asymptomatic 'healthy' blood donor carriers of HCV show that none has normal liver histology and up to 70% have chronic active hepatitis and/or early cirrhosis. Histological changes at the time of the first biopsy in patients with biochemical chronic hepatitis C also show chronic active hepatitis in the majority. Characteristic histological changes include heavy lymphocytic infiltration in the portal and periportal areas. Progression to cirrhosis is common, and in a number of countries, such as Japan, progression to hepatocellular carcinoma is an important feature of chronic hepatitis C. The mechanism underlying carcinogenesis is likely to be associated with the process of fibrosis and regeneration of liver cells, as there is no DNA intermediate in the replication cycle of HCV or integration of viral nucleic acid.

Whether the virus is cytopathic or whether there is an immunopathological element remains unclear, but a combination of factors including gender, excessive alcohol intake and coexisting viral disease (particularly hepatitis B) are important interactive factors.

Clinical features and diagnosis

Most acute infections are asymptomatic, fewer than 30% of acute infections have non-specific symptoms and some develop mild jaundice. Fulminant hepatitis has been described but is uncommon. Extrahepatic manifestations include mixed cryoglobulinaemia, membraneous proliferative glomerulonephritis and porphyria cutanea tarda.

Between 50 and 80% of patients do not clear the virus by 6 months and develop chronic hepatitis. The rate of progression of chronic hepatitis is highly variable. Chronic hepatitis C infection leads to cirrhosis within two decades of the onset of infection in at least 20% of patients. Chronic infection is also associated with an increased risk of hepatocellular carcinoma, which occurs on a background of inflammation and regeneration related to chronic hepatitis over three or more decades. The risk of developing hepatocellular carcinoma is estimated at 1–5% after 20 years, but this varies considerably in different areas of the world. Hepatocellular carcinoma develops more commonly in men than in women.

Current routine diagnostic tests for detection of antibodies to HCV are sensitive and specific and most screening tests are based on enzyme immunoassays, with confirmatory tests based mainly on recombinant immunoblot assays. The presence of antibodies to specific antigenic components of HCV is variable and may or may not reflect viraemia. Detection and monitoring of viraemia are important for management and treatment and sensitive molecular techniques are available for the measurement of HCV RNA.

The identification of specific genotypes is important, with observations suggesting an association between response to antiviral treatment with interferon and particular genotypes.

Management and treatment

Management of hepatitis C infection is difficult. The patients must be excluded from donating blood and should be advised about the known modes of transmission of the virus, particularly by the parenteral route. Alcohol may act synergistically with HCV in causing liver damage, and alcohol intake must be reduced to the absolute minimum, if any. Consideration of lifestyle risks for other viral infections such as hepatitis B and HIV infection is essential.

Treatment with pegylated interferon alpha has been shown to yield good and sustained responses in 25–40% of selected patients. Studies indicate that younger patients without cirrhosis, with genotype 2 and 3 infection, are more likely to respond to treatment for several months than patients with genotype 1, and better response is obtained in patients with a lower viral load. Combination therapy with ribavirin, a synthetic guanosine nucleoside analogue, indicates that up to 50% of patients who have relapsed after treatment with interferon alpha have a sustained biochemical and virological response to combined treatment. New specific inhibitors of HCV are being investigated, including HCV protease inhibitors, receptor agonists and nuclease-resistant ribozymes.

Prevention

Vaccines against HCV are not available, despite considerable efforts. Prevention of transmission to contacts is based on measures described for HBV and other bloodborne viruses.

HIV and AIDS

Introduction and definitions

The global pandemic of infection with the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS) has attracted more publicity and political debate than any other infection. The scale of the pandemic is illustrated by the fact that, since the original description of AIDS in 1981, AIDS has been reported in more than 190 countries, with an estimated number of HIV infections by the beginning of 1998 of more than 30 million people, with more than 2.3 million deaths in 1997 alone. The precise incidence of HIV infection in the population is not known, but the projected cumulative infections are expected to reach 40 million shortly. More recently, the pandemic of HIV has evolved into essentially an infection transmitted heterosexually in the developing and poor countries of the world, accounting now for more than 75% of all cases of AIDS, and infection of groups defined as at 'high risk' in the industrialised communities. These include young adult homosexual and bisexual males in major cities and their partners, intravenous drug abusers and their sexual partners, and persons who change their sexual partners frequently.

It should be noted that the risk to travellers depends to a large extent on their own behaviour and exposure to risk, and that the epidemic of HIV is not confined by geographical boundaries or to particular regions. There is no evidence of transmission of HIV by purely social and household contact or by leisure activities such as swimming, and there is no evidence of transmission by insects.

Nature of the infectious agent

Human retroviruses, as is the case in other vertebrates, exist in two forms: as genetic elements in chromosomal DNA (endogenous retroviruses) and as horizontally transmitted infectious RNA viruses (exogenous retroviruses). Endogenous retroviruses probably evolved from transposable elements; they are present in most vertebrates and some other life forms as DNA proviruses in the germ line, and most of these are silent or have become pseudogenes.

Exogenous retroviruses are transmissible and three are associated with human disease: *human T-cell lymphotropic virus 1* (HTLV-1) is associated with adult T-cell leukaemia and tropical spastic paraparesis, HTLV-2 is associated with hairy cell leukaemia and HIV is the cause of AIDS.

Retroviruses contain RNA genomes and replication involves transcription of the RNA genome into a double-stranded DNA intermediate by a viral enzyme referred to as reverse transcriptase.

HIV was isolated in 1983. The HIV particle is an icosahedral sphere, which is enveloped and has 72 projections consisting of two glycoproteins, gp120 and gp41. Glycoprotein 41 traverses the lipid bilayer. The matrix protein (p17) covers the internal surface of the virus, and p24 constitutes the core shell, which encloses the two copies of the single-stranded HIV RNA (Figure 7.4).

HIV uses the CD4 molecule on the surface of both immature T lymphocytes and mature CD4+ T-helper lymphocytes for initial attachment to cells. This receptor is also present in lower amounts on monocytes, macrophages and antigen-presenting dendritic cells. Other coreceptors are also present to promote the entry of the virus into susceptible cells, where, after uncoating of the virus, reverse transcription, integration and expression of the viral genome occur, followed by viral assembly and release of virus. Infected cells are ultimately destroyed by a direct cytopathic effect, but most of the cells are not killed and may therefore form an important reservoir for persistent infection with virus shedding. There are two major antigenic types of HIV, HIV-1 and HIV-2, which share approximately 40% of genetic homology. While both types cause AIDS, it appears that

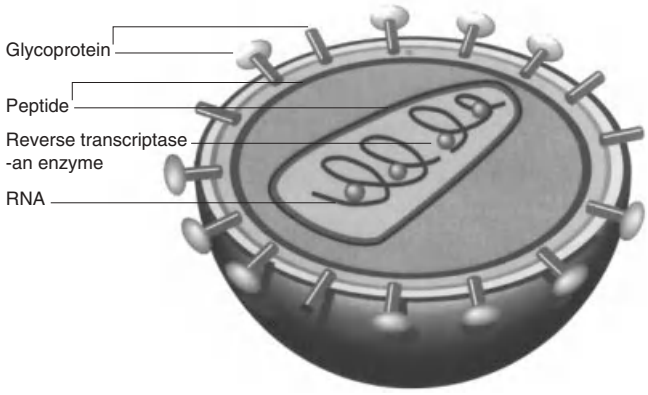

Figure 7.4 Structure of HIV.

HIV-2 is less pathogenic; it occurs mainly in West Africa and sporadically elsewhere. Phylogenetic analysis of HIV-1 has revealed at least 10 subtypes, but the more recent identification of highly divergent HIV-1 strains, principally from patients in Cameroon, led to classification of HIV-1 into two groups. The major (M) group corresponds to HIV-1 strains disseminated widely throughout the world, and an outlier group (O) corresponding to the highly divergent HIV-1 strain, identified originally in Cameroon but found subsequently in Gabon, Europe and the US.

Epidemiology and geographical distribution

The global dissemination of HIV was referred to in the introduction to this section. In industrialised countries most reported cases of AIDS occur in one or more of the following groups:

- sexually active homosexual or bisexual men (genitaloral, genital–anal and genital–genital sex)
- intravenous drug abusers
- patients with haemophilia and others with severe coagulation disorders who received unheated blood factor concentrates
- recipients of unscreened blood transfusions (in the past)
- sexual partners of the above groups
- children born to mothers infected with HIV.

Since the late 1980s there has been a substantial decrease in HIV prevalence among men who have sex with men, but an increase in heterosexual transmission, with the highest rates in women.

Another epidemiological pattern is emerging in countries of eastern Europe and the former Soviet Union, where infection with HIV has increased dramatically, mainly in association with intravenous drug abuse and unprotected sexual transmission. Nosocomial transmission of HIV accounts for more than 50% of children with AIDS in Romania and the Russian Federation. The epidemic in sub-Saharan Africa involves well over 20 million people, and an estimated 4–5 million children. The prevalence rate in the population ranges from 1–15 to 20% or more. About 7,500 people are infected daily. Infection is typically the result of heterosexual and perinatal transmission. HIV-2 is found principally in West Africa, with a prevalence of about 10%. The prevalence of HIV and AIDS is increasing dramatically in Asia, with most cases (approaching 90%) occurring in India, Burma and Thailand. Initially most infections were in intravenous drug abusers, spilling rapidly into prostitutes and their clients and into the general population. The predominant mode of spread of HIV in Asia is by heterosexual transmission. The prevalence of infection among pregnant women is increasing rapidly. The pattern of the prevalence of HIV infection and AIDS in the Caribbean and Latin America is similar to that described initially in North America, but with an apparently rapid increase in heterosexual transmission since the late 1980s.

Reservoir of infection

The reservoir of infection is humans. The origin of HIV is still debated and the distant evolutionary relationship with Simian immunodeficiency virus is being examined.

Pathology

Antigen-presenting cells which prime naive T lymphocytes form a complex system of cells referred to as dendritic cells. These cells express class I and class II molecules of the major histocompatibility complex (MHC) and specific chemokines, which act as coreceptors with CD4 molecules. CD4 permits binding of HIV-1 gp120 to cells, but the chemokine coreceptors allow fusion and penetration of the virus into the host cell. Dendritic cells are readily infected by HIV-1 and support viral replication in the presence of activated lymphocytes, and 95% of HIV-1 variants transmitted are macrophagetropic. The Langerhans cells are either infected by the virus or pick up the virus and then migrate to regional lymph nodes. The virus is disseminated rapidly throughout the lymphoid system and later enters the bloodstream and further replication occurs. After transition to the chronic phase of the disease, virus particles trapped in the follicular dendritic cell network become the dominant form of HIV-1, and the number of circulating virus particles falls. Latent infection of CD4+ T lymphocytes results in the establishment of replication-competent HIV-1 proviral DNA, a reservoir for the virus.

The intrinsic ability of HIV-1 to mutate rapidly allows the virus to escape immune surveillance and specific immune

responses so that it is able to continue to infect cells and replicate, representing, together with a stable reservoir of virus, a continuous source for infection of CD4+ T lymphocytes. CD4+ T cells are damaged in several different ways: virus replication can destroy the cell as a result of damage of the cell membrane; viral genetic material may interfere with the metabolism of the cell; and the virus may infect and destroy progenitor lymphoid cells. CD4+ T cells may also be destroyed by autoimmune reactions that kill uninfected cells, and is likely that anti-HIV immune effector cells kill many cells infected with the virus.

The number of circulating CD4+ lymphocytes correlates significantly with the development of bacterial, fungal, parasitic and viral opportunistic infections, including *Mycobacterium tuberculosis*, *M. avium* complex and *Streptococcus pneumoniae* infections, candidiasis, cryptococcosis, histoplasmosis, coccidioidomycosis, toxoplasmosis, enteric helminthic infections, *Pneumocystis carinii* pneumonia, herpes zoster, mucocutaneous herpes, polyomavirus and others. Various tumours are also found in patients with AIDS, including non-Hodgkin lymphomas, Kaposi sarcoma, cancer of the central nervous system, invasive cervical cancer and others.

Clinical features and diagnosis

Primary HIV infection is often asymptomatic but may present as an acute illness with fever, sweating, myalgia and arthralgia, sore throat, lymphadenopathy, nausea and vomiting, diarrhoea, headache and other neurological symptoms and a rash lasting between 2 and 4 weeks, but symptoms such as fatigue may persist for many weeks or months. Most patients then become asymptomatic, usually for years. The incubation period is 2–4 weeks after infection, with a range of 5–90 days or longer. Following primary infection, there may be a slow and progressive decrease in the number of CD4+ cells and an increase in CD8 + cells.

AIDS is the late manifestation of infection with HIV, characterised by a marked depletion of CD4+ cells, resulting in a reversal of CD4+:CD8+ cell ratio. The progressive immunodeficiency is accompanied by a wide range of opportunistic infections, neoplasms, and may present with AIDS encephalopathy (AIDS dementia complex) and other neurological complications that may occur in the absence of opportunistic infections. The Centers for Disease Control (Atlanta, US) definition of AIDS, adopted in the US in 1992, is helpful. The definition is based on a positive test for HIV and the following.

1 A CD4+ T cell number of less than 200/mm^3 (the normal count is 600–1000/mm^3) of whole blood or a CD4+ T cell/total lymphocytes percentage of less than 14%, or

2 A CD4+ T cell number of 200/mm^3 or more and any of the following conditions: fungal diseases, including candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, isosporiasis; *Pneumocystis carinii* pneumonia; cryptosporidosis, or toxoplasmosis of the brain, bacterial diseases including pulmonary tuberculosis and other Mycobacterium species, recurrent *Salmonella* septicaemia; viral diseases, including cytomegalovirus infection, HIV-related encephalopathy, HIV wasting syndrome, chronic ulcer or bronchitis due to herpes simplex, or progressive multifocal leucoencephalopathy; malignant diseases such as invasive cervical carcinoma, Kaposi sarcoma, Burkitt lymphoma, primary lymphoma of the brain or immunoblastic lymphoma; recurrent pneumonia due to any age.

Laboratory screening tests for HIV-1 and HIV-2 are based mostly on a variety of ELISAs based on antigens consisting of viral lysates or recombinant proteins corresponding to the immunodominant epitopes of HIV-1 (including the group 0 variants) and HIV-2. Rapid and simple laboratory tests are also used in developing countries, based on filtering serum through a membrane coated with recombinant HIV-1 and HIV-2 antigens. Confirmatory assays are generally based on Western blot techniques, but other immunoblot methods are also available. Strain serotyping methods and subtyping techniques are available. Virus isolation is carried out in high security laboratories. PCR and nested-PCR is used for the detection of proviral HIV DNA. The amount of virus in peripheral blood (viral load) is assessed by measurement of plasma RNA. p24 antigenaemia is measured by ELISA. Genotypic drug resistance assays are important for treatment and monitoring antiviral therapy.

Management and treatment

The management of the patient with HIV is dictated by the level of disease activity that is indicated by the degree of immunodeficiency and viral load; it includes the management of opportunistic infections and other syndromes associated with immunodeficiency and malignancy.

There has been rapid and substantial progress in the development and availability of specific antiviral drugs since 1987. These include nucleoside inhibitors of reverse transcriptase and the more recent introduction of protease inhibitors. The optimal treatment is by a combination of drugs with substantial clinical benefit, and several nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors and protease inhibitors are available. Treatment and virological monitoring should be carried out under the supervision of specialists. Note that HIV resistance to all classes of antiretroviral drugs has now been described and monitoring for genotypic resistance is important.

Treatment should be aimed at preventing or delaying the emergence of drug resistance.

Prevention

The key approaches are health education and prevention of infection by immunisation. Travellers are not at increased risk of infection with HIV unless they engage in risk behaviour (see below) or are exposed to unscreened or inadequately screened blood transfusion or inadequately sterilised syringes, needles and medical and surgical instruments. Unsafe sexual practices and intravenous exposure to illicit drugs pose a high risk of infection to travellers. The following explicit recommendations will reduce the risk of infection.

- Avoid mouth contact with the vagina, penis or anus.
- Avoid all sexual practices that could cause tears in the lining of the vagina, anus and rectum, or the penis.
- Avoid sexual activities with partners from high-risk groups: prostitutes (female and male), homosexual men (particularly those who change partners frequently), bisexuals and intravenous drug users (male and female).
- Avoid all other activities that involve the exchange of body fluids.
- If the health status of the partner is not known, a condom must be used for all sexual practices in which the exchange of body fluids occurs (this includes wet kissing, oral sex – either male or female), and obviously vaginal or anal sexual intercourse.

There are enormous hurdles to be surmounted in vaccine development against HIV. These include the considerable genetic heterogeneity of HIV strains and the emergence of new genetic variants; incomplete knowledge of viral–host interactions; and the practical complexity of ensuring the safety of candidate vaccines and mounting clinical trials and later efficacy vaccine studies. Nevertheless, progress is being made and the following are some candidate vaccines that have undergone clinical trial:

- recombinant subunit vaccines: gp160 and gp120
- recombinant particle vaccines: Ty-p24 virus-like particles
- recombinant virus vectors: vaccinia-gp160; vaccinia-gp160, gag, pol; canarypox gpl60; canarypox gp120TM, gag, protease; canarypox gp120 TM, gag, pol, nef
- recombinant bacteria: attenuated *Salmonella typhi* gp120
- synthetic peptides: V3 (envelope); p17 (core); V3 fused with T-cell helper gag epitope; V3 fused with T-helper env epitope; multiple V3 on polylysine backbone
- DNA-based immunisation: gp160 and rev; gag
- combination of some of the above preparations.

HIV vaccine development is a high priority but progress is likely to be slow, particularly because of the inherent difficulties associated with safety and efficacy.

Viral gastroenteritis

Introduction and definitions

Human gastroenteritis can be caused by bacteria, viruses and parasites, and diarrhoeal illness is second only to respiratory diseases in terms of morbidity and mortality, with very high mortality in children in the developing countries.

Viruses that cause human gastroenteritis belong to different virus families: rotaviruses account for about 70% of gastroenteritis in children; enteric adenoviruses approximately 12%; caliciviruses, including noroviruses and sapoviruses, 8%; and astroviruses are responsible for 8% of all cases of gastroenteritis in children. Other viruses can also infect the gastrointestinal tract in conditions of immunosuppression, but these are not considered in this section.

There are two epidemiological patterns. During childhood, viral diarrhoea occurs as an endemic disease, caused mainly by group A rotaviruses, subgroup F adenoviruses, classical human caliciviruses and astroviruses. The principal mode of transmission is by the faecal–oral route, by close contact and fomites. The second pattern is epidemic, affecting all ages, and caused mainly by SRSVs and at times by group B and C rotaviruses and by astroviruses. Infection is transmitted frequently by contaminated food or water.

Nature of the infectious

Rotaviruses

These viruses have a genome of 11 segments of double-stranded RNA encoding six structural proteins and five non-structural proteins within a wheel-like structure, as seen by electron microscopy. Group A rotaviruses, of which there are 10 serotypes, are major pathogens in humans and animals; groups B and C are not important causes of illness in infants and young children.

After neonatal or primary infection a specific serotype humoral immune response develops, but there is also partial protection against subsequent infections by other rotavirus serotypes. Second, third and fourth infections confer progressively greater protection. The immune correlates of protection from rotavirus infection (which can be without symptoms) and disease are not fully understood.

Adenoviruses

Adenoviruses are large icosohedral viruses measuring 70–80 nm in diameter, with a linear double-stranded DNA. There are more than 100 antigenic types, of which 49 distinct serotypes in six different subgroups, A–F, infect humans,

causing mainly acute respiratory disease, follicular conjunctivitis, epidemic keratoconjunctivitis, cystitis and, less frequently, gastroenteritis. Adenoviruses associated with gastroenteritis belong to subgroup F, serotypes 40 and 41.

Noroviruses and sapoviruses (human caliciviruses)

The first member of this group was recognised by immune electron microscopy, during a large outbreak of acute gastroenteritis in a school in Norwalk in the US, as a 27–35 nm particle. After cloning and sequencing of *Norwalk virus* it was classified as a calicivirus. The genome consists of a single-stranded RNA, and the name calicivirus describes a particle with cup-shaped depressions on its surface. The subsequent identification of other viruses causing gastroenteritis led to a classification based on the morphology of *Norwalk virus* and Norwalk-like viruses with a diameter of 27–35 nm now reclassified as noroviruses and sapoviruses, so-called classical caliciviruses with a diameter of 30–40 nm and astroviruses with a diameter of 28–30 nm. Picornaviruses with a 27 nm diameter and parvoviruses with a diameter of 18–20 nm are included among the 'featureless' small round viruses (SRVs).

Epidemiology, clinical features and geographical distribution

Viral gastroenteritis occurs throughout the world. The incubation period of rotavirus gastroenteritis is 1–2 days with a sudden onset of illness with watery diarrhoea lasting 4–7 days, vomiting and rapid dehydration. The spectrum of illness ranges from mild to severe. Virtually all children become infected during the first 3–5 years of life, but severe diarrhoea and dehydration occur primarily in children under the age of 3 years.

Rotavirus is also an important cause of nosocomial gastroenteritis. Rotavirus infection in adults occurs among those caring for children with diarrhoea, in travellers and in the elderly. The virus is transmitted mainly by the faecal–oral route.

The incubation period of the calicivirus group (see above) ranges from 10 to 48 h; diarrhoea, vomiting or both last for 1–2 days. The illness occurs typically in older children and adults, and is uncommon in preschool children. Outbreaks occur in schools, camps and holiday centres, hospitals, cruise ships and so on, and are associated with ingestion of contaminated drinking or recreational water (swimming pools), uncooked shellfish, eggs, cold foods and salads. The faecal–oral route alone does not, however, explain the explosive outbreaks that have been documented. Very large numbers of virus particles are present in vomit and vomiting is often projectile, so aerosol transmission, particularly in enclosed spaces, is likely.

Human astrovirus infections occur in childhood, often without symptoms, and in the elderly, and occasionally as the cause of foodborne outbreaks of diarrhoea. Transmission is by the faecal–oral route, person-to-person contact and possibly fomites. The seasonal incidence is highest during the winter.

Pathology

The pathogenesis of rotavirus infection is based on increasing necrosis of the gut epithelium, leading to loss of villi, loss of digestive enzymes, reduction of absorption and increased osmotic pressure, resulting in diarrhoea. These changes are followed by increased fluid secretion. The onset of dehydration may be rapid. Pathological changes in the ileum resulting from infection with SRSVs include blunting of intestinal villi, crypt hyperplasia and cytoplasmic vacuolation, and lymphocytic infiltration of the lamina propria.

Pathological changes observed in animals infected with species-specific astroviruses reveal infection of mature enterocytes at the tip of the villi of the small intestine.

Diagnosis

Specific diagnosis of viral gastroenteritis is relatively easy by electron microscopy and immune electron microscopy of faecal extracts. The principal routine techniques for rotavirus include ELISA and passive particle agglutination. Molecular techniques are also available. Enteric adenoviruses are detected in faecal extracts mainly by ELISA using subgroup F-specific monoclonal antibodies, and by electron microscopy and immune electron microscopy. Laboratory diagnosis of noroviruses, sapoviruses and astroviruses is by electron microscopy or immune electron microscopy, ELISA and RT-PCR.

Management and treatment

Oral rehydration with fluids containing sugar and electrolytes is most important, and in severe cases, particularly in children, rapid fluid replacement intravenously is a life-saving measure. If the ability to drink is lost, parenteral administration of fluid is a medical emergency. Oral bismuth subsalicylate has been found to be beneficial in children with acute watery diarrhoea.

Antibiotics have no place in the treatment of viral gastroenteritis and specific antiviral therapy is not available.

In general, travellers' diarrhoea does not require intensive treatment apart from general supportive measures, but blood in the stools and persistent diarrhoea longer than a

few days requires urgent medical attention and laboratory investigation.

Protective measures and prevention

General food and water hygiene measures and strict personal hygiene are important, as are sensible precautions with the consumption of food and water. Viruses causing gastroenteritis are highly contagious and spread can be rapid. Careful handwashing, personal hygiene, disinfection, and safe disposal of contaminated material and faeces are important. Outbreaks in hospitals, nurseries, holiday centres and cruise ships require meticulous application of these measures.

Attenuated live rotavirus vaccines derived from a single human wildtype serotype (HRV), and attenuated live oral pentavalent bovine-human reassortant vaccine (PRV) have been developed. Shedding of the vaccine virus in faeces occurs but considerably less frequently with the PRV preparation, and infection of immunocompromised contacts may take place, although the risk is much lower than transmission of the wild virus from unvaccinated children

Vaccines against other viruses causing gastroenteritis are not available.

Poliomyelitis and other enterovirus infections

Introduction and definitions

The enteroviruses belong to the family *Picornaviridae* (small RNA viruses) comprising five genera: enteroviruses, rhinoviruses, hepatoviruses, cardioviruses and aphthoviruses. Most infections with enteroviruses are inapparent, but some may cause serious infection of the central nervous system, heart, skeletal muscles, liver and pancreas.

Sixty-six serotypes of enterovirus have been isolated from humans and can replicate in the epithelium of the nasopharynx, gastrointestinal tract, lymphoid tissue, reticuloendothelial system and, in the case of HAV, the liver. The virus may spread to other organs and may cause severe disease, for example the central nervous system (polioviruses), the myocardium (coxsackie viruses, causing myocarditis) and others. Prevention by immunisation is limited so far to poliomyelitis and hepatitis A. From the point of view of the traveller, poliovirus and HAV are considered to be the most important of the enteroviruses. This section considers, therefore, only poliomyelitis; hepatitis A infection has been discussed earlier in this chapter. It should be noted that two genera of the Picornaviridae cause diseases of animals: the cardioviruses cause disease in mice, and the aphthoviruses cause foot-and-mouth disease of cattle.

Nature of poliovirus

All the picornaviruses have similar morphology, molecular and structural properties, and replication strategies. The virion is an icosahedral, unenveloped small particle measuring approximately 27 nm in diameter and containing a single positive strand of RNA of approximately 7,500 nucleotides. Picornaviruses multiply in the cytoplasm, and the RNA acts as a messenger to synthesise viral macromolecules. Viral RNA replicates in complexes associated with the cytoplasmic membranes.

There are three serotypes of polioviruses, 1–3. The virus enters the body by mouth and replication occurs in the oropharynx and the cells lining the alimentary tract. A viraemic phase follows. Within the central nervous system the virus spreads along nerves and extensive replication destroys motor neurons, particularly of the anterior horn cells of the spinal cord, leading to paralysis. Virus is shed from the throat and in the faeces. Faecal shedding may continue for several weeks.

Epidemiology and geographical distribution

The major route of transmission of poliovirus is faecal–oral, where sanitation and standards of hygiene are poor. Pharyngeal spread is relatively more important in areas where sanitation is good and, in the past, during epidemics in industrialised countries.

Poliomyelitis can affect all age groups. In areas with poor sanitation most infants were infected early in life and acquired active immunity while still protected by maternal antibodies. The infection occurred worldwide before the introduction of large-scale immunisation, and the highest incidence of clinical disease was in temperate zones and in the more developed countries, most commonly during summer and autumn. It was expected that poliomyelitis caused by wild-type virus would be eradicated from most (if not all) countries at the beginning of the third millennium, and it is likely that polioviruses found in nature will probably be derived from oral poliovirus vaccine strains. However, poliomyelitis remains endemic in a number of countries including Afghanistan, Pakistan and Nigeria.

The incubation period is commonly 7–14 days for paralytic cases, with a reported range of 3–35 days. Cases are most infectious 7–10 days before and after the onset of symptoms, and virus may be shed in the faeces for 6 weeks or longer.

Reservoir of infection

The reservoir of infection is human, most frequently persons with inapparent infection, especially children.

Clinical features and diagnosis

Most infections are asymptomatic or range in severity from non-paralytic fever, headache, nausea and gastrointestinal symptoms to aseptic meningitis and paralysis. Most clinical illnesses resolve without paralysis. The clinical syndrome may be biphasic, with a minor illness followed by remission, but subsequently develops into a major severe illness. Paralysis of respiratory muscles and swallowing usually threatens life. Paralysis is typically asymmetric. Case fatality rates in paralytic cases vary from 2 to 10% in different epidemics and increase dramatically with age.

Differential clinical diagnosis includes post-infectious polyneuritis, Guillain–Barré syndrome and other causes of paralysis. Differential diagnosis of acute non-paralytic poliomyelitis includes aseptic meningitis, bacterial meningitis, brain abscess and encephalitis.

Laboratory diagnosis is based on viral isolation from faecal samples 24–48 h apart, and type identification based on molecular techniques. Faecal samples should also be obtained from household and other close contacts.

It should be noted that other enteroviruses, particularly *Coxsackie virus A7* and *Human enterovirus 71*, occasionally cause poliomyelitis-like illness.

Prevention

Inactivated (Salk) and live attenuated (Sabin) vaccines have been used for mass immunisation most successfully, and WHO set a target of global eradication of poliomyelitis by the year 2000. Wild-type poliovirus transmission was eradicated from the Americas in 1991 and has been eradicated from many other industrialised countries. The risk of oral polio vaccine-associated poliomyelitis has been estimated by WHO at between 0.5 and 3.4 cases per million susceptible children. This has re-established a role for the use of inactivated vaccine, and a strategy for immunisation with the Salk vaccine is being established in the US and elsewhere. In the meantime, routine universal immunisation with the live attenuated oral poliovirus vaccine continues in the majority of countries and no adult should remain unimmunised against poliomyelitis.

Booster (reinforcing) immunisation for adults is recommended for travellers to areas or countries where poliomyelitis is endemic.

Influenza

Introduction and definitions

Influenza is a highly infectious acute respiratory disease causing epidemics and pandemics throughout the world. While it is usually a self-limiting disease, it can be complicated by bronchitis and secondary bacterial pneumonia, and in children by otitis media. Primary influenza virus pneumonia is rare but carries a high case fatality rate. Epidemics are generally associated with a large number of excess deaths among the elderly and those with underlying chronic respiratory and cardiac diseases, renal or metabolic diseases and immunosuppression. Epidemics and pandemics occur at unpredictable intervals.

There are three types of influenza virus, A, B and C. Type A causes widespread epidemics and pandemics, type B is associated with regional and widespread epidemics, and type C is associated with sporadic cases and minor local outbreaks.

Nature of the infectious agent

The influenza viruses are spherical enveloped RNA viruses measuring 80–120 nm in diameter, and filamentous enveloped particles may also occur.

The RNA genome of influenza A and B viruses consists of eight separate segments containing 10 genes, whereas influenza C virus contains only seven RNA segments. The RNA segments are complexed with nucleoprotein to form a nucleocapsid with helical symmetry, which is enclosed in an envelope consisting of a lipid bilayer with two surface glycoproteins, the haemagglutinin and the neuraminidase. Influenza C virus has a single surface glycoprotein.

The three influenza viruses are classified on the basis of the nucleoprotein, which is stable and has no serological cross-reactivity. The haemagglutinin and neuraminidase undergo genetic variation in influenza A and B viruses as a result of genetic reassortment, whereas the glycoprotein of influenza C virus is stable.

Influenza A subtypes are classified by the antigenic uniqueness of the surface glycoproteins, with the haemagglutinin designated as H and the neuraminidase as N. Fifteen subtypes of haemagglutinin (H1–H15) and nine subtypes of neuraminidase (N1–N9) have been identified, and variants are described by the geographical site of isolation, the culture number and year of isolation, e.g. A/Japan/305/57(H2N2), A/Hong Kong/1/68(H3N2), A/Sydney/5/97(H3N2), and, in the case of influenza B, B/USSR/2/87, B/Beijing/184/93, and so on. Various influenza A subtypes have been isolated from wild and domestic aquatic birds, from pigs, horses, mink, seals and whales. Animal reservoirs are believed to be the sources of new human subtypes, probably by genetic reassortment with human strains facilitated by the segmented viral genome. The emergence of completely new subtypes (referred to as antigenic shift) occurs at irregular and unpredictable intervals and only with influenza A viruses. Completely new subtypes are responsible for pandemics. A new

pandemic influenza A (H1N1) 2009 emerged in Mexico in April 2009 and has spread worldwide, causing illness primarily in younger age groups. Minor antigenic variations (antigenic drift) are associated with annual epidemics and regional outbreaks.

Epidemiology and geographical distribution

Influenza viruses are transmitted readily by airborne spread by sneezing, coughing or speaking, particularly among crowds in enclosed spaces. A single infected person can transmit the virus to a large number of susceptible individuals. Transmission also occurs by direct contact through droplet spread and also by contact with dried mucus. The incubation period is short, usually 1–5 days.

In temperate zones, epidemics tend to occur during the winter months (northern hemisphere from November to March, southern hemisphere from April to September), and in the tropics influenza can occur throughout the year, but often in the rainy season.

Age-specific attack rates during an epidemic reflect existing immunity from past experience with strains related to the epidemic subtype and the extent of exposure, so that the incidence of infection is often highest in children of school age.

Reservoir of infection

Humans are the reservoir for human infections, and animal reservoirs (see above) are believed to be the sources of new human influenza A subtypes. A recent example is avian influenza A (H5N1) virus, which crossed the species barrier. This virus is highly pathogenic and has caused many human fatalities in a number of countries, and remains a pandemic threat.

Pathology

Influenza viruses replicate in the columnar epithelium cells of the respiratory tract. The viruses attach to permissive cells through the haemagglutinin subunit, which binds to cell membrane glycoproteins or glycolipids containing the viral receptor *N*-acetylneuraminic acid. Replication of the virus is completed within about 6 h and kills the host cell, and desquamation of the superficial mucosa occurs. Virus is shed together with desquamated cells through the respiratory tract by mucociliary transport. Virus can be recovered from respiratory secretions for about 3–8 days. Viraemia is rare.

Occasionally, the infection may involve the alveoli, resulting in interstitial viral pneumonia, which is associated with a high mortality. In most cases with pneumonia, the pneumonia is caused by secondary bacterial infection.

Clinical features and diagnosis

The clinical picture is of abrupt onset of fever, malaise, headache, sore throat, myalgia, coryza and a dry cough lasting 2–5 days. The clinical features in children and in the elderly may differ in some respects and children may present with febrile convulsions, conjunctivitis, croup, otitis media, bronchitis and gastrointestinal symptoms. Diagnosis based on clinical presentation is difficult but more likely if influenza is known to be common in the community.

Specific diagnosis is based on viral isolation by culture, detection of viral antigens in nasopharyngeal cells by immunostaining or in respiratory secretions by ELISA, detection of viral nucleic acid and by antibody tests of paired samples showing a rise in specific antibody by haemagglutination inhibition, ELISA, complement fixation and neutralisation. Rapid bedside diagnostic tests are expected to be introduced shortly.

It should be noted that virus isolation is critical in outbreaks in order to characterise the virus fully and identify antigenic shifts and drifts. Precise characterisation of the virus is essential for the formulation of vaccines for the following year.

Management and treatment

Management is symptomatic in uncomplicated cases, but specific antiviral drugs are available and are indicated under certain circumstances.

Amantadine and rimantadine have 70–90% efficacy in preventing influenza A if given prophylatically to adults or children during the period of exposure to the virus. These drugs are not free of side effects and viral resistance may emerge during treatment. Rimantadine has fewer side effects than amantadine. These drugs may be given prophylactically for individuals who had not been vaccinated and are in high-risk groups for complications (see below). The drugs may be used therapeutically and will ameliorate the severity and duration of illness if given within 48 h of the onset of symptoms.

Newer drugs that inhibit specifically the neuraminidase of both influenza A and B are available and have been licensed in a number of countries (Zanamavir or Relenza, which is administered by inhalation). Zanamavir (Relenza) is effective in preventing influenza in healthy adults, and when given therapeutically within 36 h of the onset of illness,

reduces the duration of illness by 1–2 days. Oseltamivir (Tamiflu) is a similar drug that is administered orally.

Prevention

Inactivated influenza vaccines have been used for some 40 years; they provide protection against illness in 50–90% of healthy young adults but this may be lower in other groups, such as the elderly. The vaccine strains are grown in eggs (and therefore contraindicated for individuals with egg allergy) and formulated according to the prevailing current strains. In addition to the current 2010 seasonal vaccine, vaccines against the pandemic influenza A (H1N1) 2009 virus have been developed and used worldwide.

The risk of influenza during travel varies and depends on the time of year and destination (see above), and contact with people from different parts of the world where influenza may be prevalent. Influenza can be a severe illness, especially in groups at high risk of developing complications. These include the following:

- persons 65 years old or older
- residents of nursing homes and any other long-term care facilities that house persons of any age who have chronic medical conditions
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including children with asthma
- adults and children who have the following medical conditions:
  - chronic metabolic diseases (e.g. diabetes mellitus)
  - renal dysfunction
  - haemoglobinopathies
  - immunosuppression
- children and teenagers (aged 6 months–18 years) receiving long-term aspirin therapy
- women who will be in their second or third trimester of pregnancy during the influenza season.

Vaccine is also recommended for the following groups:

- healthcare personnel
- employees of nursing homes and long-term care facilities who have contact with patients or residents
- providers of home care to persons at high risk
- household members (including children) of persons in high-risk groups.

The following should also consider vaccination before travel:

- those travelling to tropical areas at any time of the year if they have not been immunised against influenza during the most recent autumn or winter
- those travelling in a large organised tourist group (e.g. on cruise ships, long-haul buses) at any time of the year. Live attenuated, cold-adapted influenza virus vaccines that are administered intranasally are in use in Russia and are under development in Australia, the US and elsewhere.

SARS

The severe acute respiratory syndrome (SARS) was identified as a new infectious disease following some 305 cases of atypical pneumonia in mid-November 2002 in the Guandgong Province of China. Rapid spread of the infection followed resulting in more than 8,000 cases and 780 deaths reported from 29 countries across five continents by July 2003. The last cases of infection were reported in China in April 2004.

Nature of the infectious agent

A novel coronavirus (SARS-CoV) was identified rapidly as the cause of the infection by classical virological methods of virus isolation and electron microscopy followed by molecular diagnostic techniques and sequencing of the viral genome.

In passing, it is interesting to note that human coronaviruses were considered hitherto as responsible for approximately 25% of human common colds, while the first coronavirus isolated some 50 years ago was infectious bronchitis virus of chickens.

Epidemiology

Early during the course of the SARS outbreak in 2002–03, an epidemiological link was established rapidly with live small animal markets in southern China selling small mammals as exotic foods for human consumption. A virus closely related to SARS-CoV was identified in palm civets. However, there is evidence that civets are not the natural reservoir of SARS-CoV since a similar virus has been found in bats and others small animals. A high prevalence of antibody to SARS-CoV was found in persons working in small animal markets in southern China.

Human-to-human transmission is not common. However, a few patients appear to have been 'super spreaders', although a combination of host factors and environmental features facilitated transmission, particularly in hospital settings. Respiratory droplets are the principal vehicles of transmission. A large outbreak also occurred in a housing estate in Hong Kong believed to have resulted from infected faecal aerosols in the sewage system of a high-rise building. Two laboratory-acquired infections have been reported.

Clinical features

Most patients become ill within 2–10 days after exposure. Clinical features include dry cough, often without upper

respiratory tract symptoms, and/or dyspnoea. Pneumonia develops by day 7–10 of the illness. Most patients have lymphopenia. The overall case fatality rate is 10%, and this may increase to more than 50% in patients older than 60 years.

Diagnosis is based on pneumonia confirmed radiographically, history of travel to affected areas in China, Hong Kong or Taiwan, or close contact with an ill person with a history of recent travel to Southeast Asia, or employment with a risk of exposure to SARS-CoV, and laboratory confirmation (a high security level 3 biosafety laboratory is required).

Prevention

SARS has been contained since 2004. The sale of civets in animal markets in southern China is banned. Travellers should avoid visiting animal markets in affected areas. Other precautions are those for influenza and other respiratory infections.

The possibility of new SARS outbreaks should not be overlooked, as it is possible that the infection may emerge again after adaptation to human transmission from bats or other small mammals.

Genital herpes

Introduction and definitions

Herpesviruses are disseminated widely in nature and infect most animal species. Eight herpesviruses have been isolated from humans so far: *Human herpesvirus 1* (HHV1; *Herpes simplex 1*, HSV-1); HHV-2 (*Herpes simplex 2*, HSV-2); HHV-3 (*Varicella-zoster virus*, VZV); HHV-4 (*Epstein–Barr Virus*, EBV); HHV-5 (*Human cytomegalovirus*); and HHV-6, -7 and -8.

Herpesviruses share a number of biological properties, including the ability to code for a large number of enzymes involved in nucleic acid metabolism; synthesis of viral DNA and capsid assembly take place in the nucleus, and the viral envelope is acquired during migration from the nucleus; production of infectious virus is accompanied by cell destruction, and the herpesviruses establish latent infection in the host.

The herpesviruses affecting humans are probably the viruses that have been studied most extensively. Genital herpes, caused most frequently by HSV–2 but also by HSV–1, is the most relevant to the traveller.

Nature of the infectious agent

The herpes simplex viruses belong to a family of large enveloped DNA viruses, measuring 120–300 nm, containing linear double-stranded DNA. HSV-1 and HSV-2 are closely related, with approximately 70% genomic homology.

HSV-1, HSV-2 and VZV form a subfamily named the *Alpha herpesvirinae*, characterised by a very rapid reproductive cycle, rapid destruction of the host cell and ability to multiply in a variety of host tissues. These viruses establish latent infection in the dorsal root ganglia. Reactivation of latent virus is associated with stimuli such as stress, menstruation and ultraviolet light, in the presence of a fully developed immune response, the production of recurrent infection and virus shedding. Reactivation may occur at intervals throughout life.

Epidemiology and geographical distribution

HSV is disseminated throughout the world and is endemic in all the human populations examined. Humans are the only natural host. Transmission of the virus is by direct contact between a susceptible person and an individual shedding the virus. Transfer of the virus occurs by infection of a mucosal surface or by entry through skin abrasions and lesions such as cuts. Replication of the virus occurs at the site of infection, followed by a short period of viraemia. The primary infection is usually asymptomatic.

The site of primary infection for HSV-1 is most frequently the oral cavity and oropharynx, often by kissing, and by early adult life infection rates are in the order of 90–95%. The site of infection for HSV-2 is the genital mucosa and transmission is by intimate sexual contact. However, HSV-1 and HSV-2 may infect at either of these sites (between 10 and 40% of primary genital infections may be caused by HSV-1). It should be noted that although infection with HSV-2 is transmitted sexually, seroprevalence rates of about 30–60%, which increase with sexual maturity, do not attain the levels of infection with HSV-1. Seroprevalence of HSV-2 is related to socioeconomic factors but particularly to the number of sexual partners.

Previous infection with HSV-1 does not protect against HSV-2, but those who have been infected with HSV-1 usually experience milder symptoms with HSV-2 compared with those who have not experienced either form of the virus.

Transmission is by direct contact with infected secretions, obviously when genital lesions are present; however, the virus can be excreted asymptomatically and this may occur in 2% of women. The presence of viral DNA, detected by PCR in genital swabs, in the absence of virus from women with a history of recurrent genital herpes suggests persistent viral infection (chronicity) rather than recurrent infection. Nevertheless, about 60% of those infected with HSV-2 will report recurrent infection.

The incubation period is 2–20 days, with an average of about 1 week.

Pathology

Pathological changes in the skin include ballooning of infected cells, cell degeneration, formation of multinucleated giant cells, inflammatory changes, and the accumulation of vesicular fluid between the layers of the epidermis and dermis. The vesicular fluid contains large quantities of virus. Scarring after healing is uncommon. Vesicles are less prominent, in general, when mucous membranes are infected. Shallow ulcers are more common as the vesicles rupture rapidly because of the thin layer of protective stratified epithelium. The intensity of the inflammatory response is significantly less marked with recurrent disease.

Clinical features and diagnosis of genital HSV infection

Primary genital infection is frequently a severe clinical illness lasting 3 weeks or longer. The primary disease is associated with fever, malaise, bilateral inguinal lymphadenopathy and pain, which can be very severe. In women, the infection usually involves the vulva, vagina and cervix. The lesions may extend to the perineum, the upper thigh and the buttocks. Women frequently have dysuria and urinary retention due to urethral involvement and cystitis. In men, lesions are found on the glans penis, the prepuce or the penile shaft. Perianal and anal infections are common in homosexual men.

Complications include aseptic meningitis in 10%. Sacral radiculomyelitis with associated neuralgias may occur in both men and women. Resolution of the symptoms of primary infection may extend over several weeks.

Recurrent genital herpes is a milder disease in comparison with primary infection, but it is distressing nevertheless. A limited number of vesicles appear and localised irritation is a more prominent feature than pain. The frequency of recurrence varies from patient to patient. It is estimated that approximately 30% have no recurrences, 30% have about three recurrences each year, and the remainder more frequent recurrences.

Diagnosis in the laboratory is by viral isolation by culture, direct or indirect immunofluorescence, immunoperoxidase techniques, enzyme- and radioimmunoassays and nucleic acid detection.

Treatment

The treatment of choice of skin and mucous membrane lesions is with 5% acyclovir triphosphate in an aqueous cream base. Severe orofacial herpes and severe genital herpes are treated with oral acyclovir for 5 days. Prevention of overt recurrent infection is by oral acyclovir given over prolonged periods of months. Systemic infections are treated by slow intravenous infusion of acyclovir.

Prevention

Vaccines for HSV-1 and HSV-2 are under clinical evaluation. Other methods for prevention are those that apply to reducing the risk of contracting sexually transmitted infections, including the frequency of sexual contact, the number of sexual partners, particularly those who change sexual partners frequently (prostitutes, sexually active homosexual men), and safe sex (activities that do not allow exchange of body fluids, including consistent and correct condom use and other mechanical barriers). Medical advice must be sought if symptoms develop.

Rabies

Introduction and definitions

Rabies is a viral infection that is transmitted in the saliva of infected mammals; it causes an acute encephalomyelitis that is almost always fatal. Human pathogens of medical importance are members of the genus *Lyssavirus* and *Vesiculovirus*. Almost all cases of human rabies, a lyssavirus infection, are caused by a bite from a rabid animal. The risk of rabies is highest in countries of most of Asia, Africa and South America, and it is rare as a human infection in western Europe and North America, but every year up to 40,000 people receive post-exposure prophylaxis in the US.

Nature of the infectious agent

Rabies virus is a member of the family *Rhabdoviridae*, with a characteristic bullet shape. There are some 80 other bullet-shaped viruses that infect animals (including fish), plants, invertebrates and insects. For practical purposes, only *Rabies virus* is considered below, but other members of the *Lyssavirus* group, which include the serologically related *Lagos bat virus*, *Mokola virus* and *Duvenhage virus* in Africa, and Duvenhage virus in Europe (European bat virus), should be noted.

Rabies virus is a negative-sense, non-segmented, single-stranded RNA virus measuring about 75×180 nm. The helical nucleocapsid of 30–35 coils is surrounded by an outer

lipid bilayer membrane with surface projections about 8 nm in length. The viral genome encodes five proteins, three of which are associated with the ribonucleoprotein complex, which, together with the viral RNA, aggregate in the cytoplasm of infected neurons to form the characteristic Negri bodies. The matrix protein (M) and the glycoprotein (G) are associated with the viral envelope. The glycoprotein is required for virus infectivity and recognises specific cell receptors. It is also the only rabies virus protein known to induce neutralising antibody.

The effect of chemical agents on rabies virus is underlined by the importance of thorough cleansing of the wound with soap or detergent. The virus is destroyed by quaternary ammonium disinfectants, 1% soap solutions, ionic and non-ionic detergents, 5% iodine, common organic solvents such as 45% alcohol, ether and chloroform, formalin and β-propriolactone.

Isolates of rabies virus from naturally infected animals, i.e. wild-type virus, are referred to as 'street' virus, and viruses adapted by laboratory passage in animals or cell culture are referred to as 'fixed' virus.

Epidemiology, geographical distribution and reservoir of infection

Human rabies is almost always caused by a bite or contamination of surface wounds by virus in saliva, but infection through intact mucosa, for example of the mouth or the conjunctiva, can occur. Aerosol transmission has been implicated in human infection in bat-infested caves and in laboratory accidents. Human-to-human transmission has been reported rarely, for example by transplantation of infected corneas, and in the older literature. Rabies has not been reported in nursing and medical staff, but nevertheless there is a risk of exposure by bite or by contaminated saliva during airway care, and appropriate precautions should be exercised. It should also be noted that definitive animal exposure or incident cannot be identified in a significant number of human cases.

Rabies is primarily a disease of animals and most human cases occur in the developing world. The only areas free of animal rabies include Australia and New Zealand, and islands such as the UK and Ireland, and the Pacific Islands. Rabies is most prevalent among wild foxes, wolves and jackals, followed by domestic dogs, skunks, cats, farm animals, bats and others. The principal reservoir in Africa, Central America (including Mexico), South America and Asia is the unvaccinated domestic dog. There is little information about rabies in wildlife in tropical areas. The major reservoir of infection in Europe is the red fox, and rabies has been identified in Central European deer. The major sources in the US include skunks, bats and racoons.

Pathology

Although rabies virus receptors appear to coincide with the distribution of acetylcholine receptors, the virus can enter the cell independently of these receptors. The virus may access the peripheral nerves directly or it may replicate in the muscle tissue, remaining at or near the site of introduction into the host for most of the incubation period, essentially at motor endplates, replicating in monocytes and later involving the peripheral nerves via the neuromuscular junctions. The virus then moves centripetally to the central nervous system for replication. Subsequently it moves centrifugally to many tissues, including the salivary glands. Pathological changes in the brain are not profound, apart from the pathognomonic Negri bodies. Few neurons are involved, there is limited tissue necrosis and some perivascular cuffing.

Clinical features and diagnosis

The incubation period is variable, ranging from a few days to several years, but in most cases the range is 30–90 days. The development of the infection depends on the severity of the exposure, the site of the bite and whether the wounds were inflicted through bare skin, and other factors.

Prodromal symptoms are non-specific, although behaviour disturbances are often present, including anxiety, depression, hyperactivity, aggression, intolerance to tactile, auditory and visual stimuli, or delirium. Later symptoms of acute encephalitis appear, and clinical features may be confused with tetanus or cerebral malaria, poliomyelitis, botulism or others. Clinical neurological findings have been classified as either 'furious' or 'paralytic'. Furious rabies is the most common form; it is characterised by spasms in response to external stimuli, which may be tactile, visual, auditory or olfactory, and include hydrophobia and aerophobia. Spasms alternate with periods of calm and lucidity, agitation and confusion and dysfunction of the autonomic nervous system. Paralytic rabies involves clinical features ranging from paralysis of one limb to quadriplegia. The disease progresses to severe neurological complications, coma and death. Clinical differential diagnosis of rabies should be considered in every patient with unexplained encephalitis or with neurological signs, particularly where there is a history of animal bite or possible exposure in a country where rabies is endemic.

Diagnosis in the laboratory is established by the detection of rabies antigen, antibody, rabies viral RNA or the isolation of the virus. Rapid diagnosis antemortem is by detection of rabies antigen by direct immunofluorescence in a skin biopsy from the nape of the neck. Other freshly obtained tissues may be used. The virus can be isolated in tissue culture by inoculation of a murine neuroblastoma cell line (NAC 1300)

or by inoculation of laboratory rodents. PCR and other molecular tests can be employed. Detection of rabies virus neutralising antibody by a rapid fluorescence focus inhibition test in the serum of unvaccinated persons is also diagnostic, and the presence of antibody in the cerebrospinal fluid (CSF) confirms the diagnosis. In vaccinated individuals differentiation between antibody due to vaccination or disease is not possible, but vaccination does not typically produce CSF antibody.

Management, treatment and prevention

The basic approach to the control of rabies is control of infection of animals where possible, prevention of exposure and immunisation. Treatment of human rabies is based on post-exposure management of the wound and prophylaxis.

Methods for the control of rabies in animals are described in a compendium prepared by the National Association of State Public Health Veterinarians of the USA [1].

Note that an unprovoked attack by an animal is more likely than a provoked attack to indicate that an animal is rabid and great care must be exercised to avoid contact with stray or unvaccinated dogs, cats and ferrets, particularly in countries where rabies is endemic and vaccination of domestic animals is unlikely.

Treatment of wounds and post-exposure immunisation

Attack by a rabid animal constitutes a medical emergency. Immediate and thorough washing of all bite wounds and scratches with soap and water and, if available, a virucidal solution as described above, such as quaternary ammonium disinfectants, ionic and non-ionic detergents or 5% iodine, are most important. Avoid closure of the wound surgically unless suture of a large wound is essential because of the size of the wound, the potential for bacterial infection and cosmetic reasons.

Post-exposure anti-rabies immunisation should include the administration of both passive antibody in the form of specific anti-rabies immunoglobulin and active vaccination with a cell culture vaccine. A desirable post-exposure prophylaxis regimen is described in the recommendations of the US Advisory Committee on Immunization Practices [2]. Briefly, in those not previously vaccinated against rabies, immediate wound cleansing must be followed by:

- administration of 20 IU/kg body weight of antirabies immunoglobulin. If feasible anatomically, the full dose should be infiltrated around the wounds, and any remaining amount should be given intramuscularly but at a distant site from the site of vaccine administration
- human diploid cell vaccine, rabies vaccine adsorbed or purified chick embryo cell vaccine should be given intramuscularly into the deltoid muscle – 1.0 ml immediately and on days 3, 7, 14 and 28.

In the case of a patient who has been vaccinated previously with any of the above vaccines or with any other type of rabies vaccine, and a documented history of antibody response to the prior vaccination, the following regimen applies after immediate wound cleansing.

- Antirabies immunoglobulin should not be given.
- Human diploid cell vaccine, rabies vaccine adsorbed or purified chick embryo cell vaccine should be given intramuscularly into the deltoid muscle immediately (day 0) and on day 3 in a dose of 1.0 ml. The gluteal muscles should never be used because the resulting antibody titres are lower than those achieved by administration into the deltoid muscle.

Primary vaccination or pre-exposure vaccination

Pre-exposure immunisation should be offered to high-risk groups, which include veterinary surgeons and veterinary nurses and assistants, animal handlers, wildlife keepers and handlers, and certain laboratory workers. Pre-exposure immunisation should be considered for other persons who may come into frequent contact with animals potentially infected with rabies or who travel to or reside in areas where animal rabies, particularly dog rabies, is enzootic and immediate access to appropriate medical care is or may be limited.

Primary intramuscular vaccination involves three 1.0 ml injections of one of the vaccines listed above given intramuscularly into the deltoid muscle on days 0, 7, and 21 or 28. Intradermal primary vaccination of three 0.1 ml doses of human diploid cell vaccine, one each on days 0, 7, and 21 or 28 is an alternative schedule.

Note that malaria prophylaxis with chloroquine phosphate (and possibly structurally related compounds, which have not yet been investigated for this effect) decreases the antibody response to anti-rabies human diploid cell vaccine given concomitantly.

Pre-exposure booster doses of vaccine must be given to laboratory research workers working with rabies virus or those in vaccine production units. Rabies antibody should be measured every 6 months and a booster dose given according to the neutralisation antibody titre.

Yellow fever

Introduction and definitions

Yellow fever is a disease of antiquity that originated most probably in equatorial Africa and was brought by the slave trade to the great cities of the New World late in the

seventeenth century (New York in 1668, Boston in 1691), although it did not reach Europe until the eighteenth century, with extensive epidemics associated with a high mortality of more than 60%. Urban and jungle yellow fever now occur only in parts of Africa and South America (apart from the rare imported case, e.g. Germany in 1999). Urban yellow fever is an epidemic viral infection of humans transmitted by the *Aedes aegypti* mosquito in the Americas and Africa from infected to susceptible persons. Although *Ae. aegypti* is the important vector in Africa, several other species of mosquito are involved. Jungle yellow fever is an enzootic viral disease transmitted among non-human primates (and occasionally humans, e.g. forest workers) by various mosquito vectors. Yellow fever virus (YFV) is a member of the family *Flaviviridae*, genus *Flavivirus*, classified in the past in the togaviruses. The other two genera in this family are *Hepacivirus* and *Pestivirus*, which include important animal pathogens such as *Bovine diarrhoea virus* and *Hog cholera virus*. The medically important flaviviruses are often associated with three major clinical syndromes: haemorrhagic fever with hepatitis (*Yellow fever virus*); encephalitis (*St Louis encephalitis*, *Japanese encephalitis*, *Powassan* and *Tick-borne encephalitis viruses*); febrile illness with rash (*Dengue virus*); and haemorrhagic fever (*Kyasanur Forest disease virus* and sometimes *Dengue virus*).

Nature of the infectious agent

Yellow fever virus is the type species of the genus *Flavivirus*. The virus particles are spherical and enveloped with a diameter of 40–50 nm. The nucleic acid consists of a single molecule of positive-sense single-stranded RNA. The virus replicates in the cytoplasm of the cell in association with the rough and smooth endoplasmic reticulum. Viral particles accumulate within lamellae and vesicles, and replication is associated with the proliferation of intracellular membranes. The high lipid content of the viral envelope is derived from the host cell membrane.

Epidemiology and geographical distribution

Yellow fever occurs in tropical Africa and tropical America between the latitudes of 16°N to 10°S in Africa and 10°N to 40°S in the Americas (Figure 7.5). It has not been seen in Asia or Australasia. Extensive epidemics of yellow fever occurred in recent years in Africa, e.g. Nigeria (1986–88), Angola (1988), Cameroon (1990) and elsewhere. The largest epidemic recorded took place in Ethiopia (1960–62) with 30,000 deaths of 100,000 clinical cases. Jungle yellow fever remains endemic in Bolivia, Brazil, Colombia, Ecuador, Peru, Panama, Venezuela and the Guyanas.

Figure 7.5 Geographical distribution of *Yellow fever virus*.

The transmission cycles of yellow fever and the interrelationships of its vectors and hosts are complex. YFV in Africa and South America has two distinct epidemiological patterns: jungle (sylvan) yellow fever and urban yellow fever. Jungle yellow fever is maintained among canopy-dwelling monkeys and tree-hole-breeding mosquitoes (*Aedes* species in Africa and *Haemagogus* species in South America). The monkey is a transient host because of the short period of viraemia, and the major amplification host is the mosquito, which is infected for life and which is also able to pass the infection transovarially. Human disease occurs sporadically or in small outbreaks and initially only in persons exposed to forest mosquitoes (the enzootic forest cycle).

The jungle yellow fever cycle now represents the most important epidemiological form of yellow fever in relation to human infection. Outbreaks are frequent when forest mosquitoes invade adjacent plantations, forest clearings and villages on the fringes of rain forests and riverine gallery forests. Human-to-human transmission by the highly efficient urban *Ae. aegypti* mosquitoes sustains the epidemics. The expansion of *Ae. aegypti* habitat, particularly in the Americas, raises the possibility of major epidemics, similar to those described in tropical Africa. Note that species other than *Ae. aegypti* may be involved, e.g. *Ae. simpsoni*, *Ae. africanus* and others.

The urban yellow fever cycle is generally maintained by *Ae. aegypti* and re-infestations in towns and villages in South America raise concerns about a resurgence of urban yellow fever, as is the case in towns and rural villages in tropical Africa.

The incubation period of yellow fever is usually 3–6 days but may be longer. Death occurs 7–10 days after the onset of illness, with a fatality rate in indigenous populations in endemic areas of generally 5% (but may be considerably higher) and 50% or more in non-indigenous non-immunised adults.

Reservoir of infection

The reservoirs of infection in forests are vertebrates, mainly monkeys and possibly marsupials and forest mosquitoes. Transovarian transmission in mosquitoes may contribute to the maintenance of infection. In urban areas, humans and *Ae. aegypti* mosquitoes are the reservoirs.

Pathology

The acute infection in both humans and animals varies in its severity from a subclinical infection to a rapidly fatal form of the disease. Consequently, description of the pathological lesions is based principally on the findings in fatal cases. The outstanding characteristic lesion of yellow fever is selective necrosis of highly specialised epithelial cells in any affected organ or in myocardial cells. Stromal cells are not involved and there is a striking absence of inflammatory cell response in or around the necrotic lesions.

The hepatic lesion in humans is characteristic. There is diffuse, severe, non-inflammatory necrosis of the parenchymal cells, classically affecting the cells occupying the midzones of the lobule. Necrosis, however, may be scattered throughout the liver lobules. Acidophilic masses of necrotic cells are intercalated with surviving cells, and necrotic hyaline cells in the liver have been termed 'Councilman bodies' (Figure 7.6). Fatty changes in the cells tend to be highly variable but they are always present. Haemorrhages in the liver are not usually found. In patients who recover, there is complete replacement of necrotic tissue by regeneration. There is no proliferation of connective tissue elements and no permanent scarring of the liver.

The recognition of the diagnostic lesion in the liver led to the development of the viscerotome for the easy and rapid removal of liver tissue from persons who had died from a febrile illness. A viscerotomy service was organised and several hundred thousand specimens were collected and examined. This systematic collection and examination of liver fragments established the epidemiology of yellow fever and resulted in the appreciation of the importance of yellow fever in the populations of endemic regions. Later, it also played an important part in the control of the disease.

The lesions in the kidneys may be as important clinically as those in the liver. The necrotic process involves principally the epithelial cells of the proximal and distal convoluted tubules and there is a variable degree of fatty degeneration affecting, somewhat irregularly, the whole of the renal tubular system. Many hyaline and granular casts are present in the collecting tubules, and calcareous masses containing calcium salts and appreciable amounts of iron are found in the loops of Henle. Vascular congestion is usual but haemorrhages into the glomerular spaces are rare. In the later stages of the disease there may be appreciable bile staining of the tubular epithelium, as well as the formation of bile casts within the tubules.

Examination of the heart reveals a soft and usually yellow-tinged myocardium with some subendocardial haemorrhages and patchy subendocardial fatty changes. Microscopically there is fatty degeneration and fatty infiltration of the cardiac fibres, and necrosis of the nuclei is often found. These changes may also affect the cells of the sinoauricular node and the bundle of His. Once more, there is a striking absence of any inflammatory cell response.

Encephalitis is not part of the picture of naturally occurring yellow fever in humans, except with neurotropic strains of the virus.

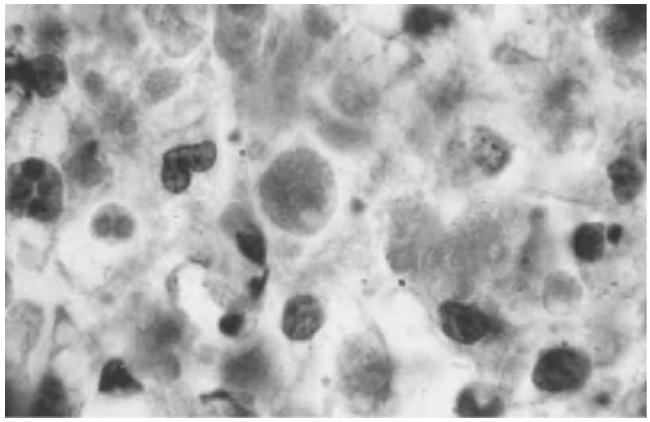

Figure 7.6 Typical Councilman bodies in the liver of a patient with yellow fever. (Courtesy of the World Health Organization)

Clinical features and diagnosis

The disease is extremely variable in severity and many mild and clinically unrecognisable cases occur. The classical triad of symptoms, namely jaundice, haemorrhages and severe proteinuria, is present only in severe infections.

The disease may be divided into three stages:

1 the initial fever,
2 the 'period of calm'
3 the period of reaction (in severe cases).

The initial fever is usually sudden in onset and lasts from 3 to 4 days with the maximum temperature generally attained within 36 h. Severe headache, often with photophobia, is frequently a prominent feature. Muscle pains are usual in the loin, back and legs, and these may be quite severe. The presence of epigastric pain is almost invariable. As the disease progresses, the Faget sign appears, namely a falling pulse rate with a constant temperature or a slow constant pulse rate with a rising temperature, stressing the lack of correlation

between temperature and pulse. During the 'period of calm', which occurs at about the fourth day and may be entirely absent, there is considerable amelioration of the symptoms and complete recovery may follow. In the third stage, the temperature rises again and jaundice appears, first in the sclera, followed by a yellowish tinge of the skin. The gums are swollen and tend to bleed readily on pressure; the tongue is coated but with red edges and tip. The liver is tender but usually not enlarged. The spleen is not palpable. Hiccough may be a very distressing feature, and black vomit, diarrhoea and skin petechiae may occur. Marked bradycardia is characteristic and the blood pressure is low. Haemorrhages may occur in almost any organ. Severe albuminuria is constant, almost from the onset, and oliguria and anuria occur during the terminal stages.

In the malignant form, hyperpyrexia may occur and profuse haemorrhages, black vomit, melaena, purpura, jaundice, disturbances of the central nervous system and anuria may develop by the third day of illness. Delirium and severe toxaemia are present before death.

The overall fatality rate in yellow fever is between 5 and 10% of all diagnosed cases, but it may be higher in a given epidemic and in non-indigenous cases. Relapses are unknown and immunity is usually permanent.

Difficulties in differential diagnosis may be experienced in atypical cases.

Malaria and relapsing fever are usually associated with splenomegaly. Blood smears will reveal malaria parasites or treponemata. Viral hepatitis may present difficulties, but on the whole jaundice is often deeper, proteinuria is uncommon and by the time jaundice appears, the patient is generally afebrile with subjective clinical improvement.

The liver is enlarged and tender. Leptospirosis is differentiated by laboratory tests. Dengue fever may mimic yellow fever closely, but proteinuria is very much less severe and jaundice is very rare. The rash of dengue also distinguishes it from yellow fever. Other haemorrhagic fevers should be considered.

Laboratory diagnosis is based on viral isolation from the blood in the first three days and by serological tests such as ELISA using monoclonal antibodies. Antibodies appear within 1 week of onset. Liver biopsy is contraindicated in acute yellow fever. Histopathological changes in postmortem material are no longer regarded as diagnostic.

Management and treatment

There is no specific treatment. Blood and body fluid precautions are required, and access of mosquitoes is prevented by bed nets and spraying with insecticides. Vaccination of contacts is required. Spraying with insecticides and aerial spraying, where possible, are important, and eliminate, or apply larvicide to, all actual and potential breeding places of *Ae. aegypti* in urban outbreaks.

Prevention

Control of yellow fever has been attained by immunisation and by vector control; however, re-infestation of villages and towns adjacent to forests with *Ae. aegypti* raises concerns about the re-emergence of urban yellow fever.

Yellow fever vaccine is a live attenuated freeze-dried preparation of the 17D strain of YFV grown in leucosis-free chick embryos. The French neurotropic vaccine developed by passage in mouse brain is no longer used. The vaccine should be stored at 2–8°C and protected from light. The diluent supplied with the vaccine should be stored below 25°C but not frozen. After reconstitution, the vaccine should be kept cool, protected from light and used within 1 h. Any unused vaccine should be destroyed by disinfection or incineration. A single dose of 0.5 ml is given subcutaneously and provides long-lasting immunity in 99% of recipients. Immunity persists for at least 10 years and probably for life, but international regulations require a booster every 10 years.

Side effects of immunisation include mild fever, myalgia and headache, which occur in less than 5% of recipients. Hypersensitivity reactions may occur in individuals allergic to egg protein. Encephalitis is extremely rare.

Contraindications include patients undergoing immunosuppressive treatment and with impaired immunological mechanisms, including malignant conditions involving the reticuloendothelial system, and lymphoma and leukaemia. Individuals infected with HIV should not be vaccinated. Under these circumstances a letter of exemption is necessary for countries where a yellow fever certificate is required. Infants under 9 months of age should only be immunised if the risk of yellow fever is unavoidable. Pregnancy is a contraindication because of a theoretical risk of fetal damage, but the risk of yellow fever in a high-risk area outweighs any risk of immunisation.

A yellow fever vaccination certificate is now the only certificate that is required for international travel to and from endemic regions.

Dengue fever

Introduction and definitions

Dengue virus is at present the most important arboviral cause of illness and death in humans. The four serotypes of *Dengue virus*, a subgroup of the genus *Flavivirus*, are distributed widely throughout the tropics and warm climate regions of Africa, Asia, Australia, the Pacific Islands, India,

the Caribbean Islands and the Americas, involving several million people each year. The incidence of the disease corresponds to the distribution of the principal vector, the *Ae. aegypti* mosquito, which maintains the virus in a human–mosquito–human cycle. The incidence of dengue is increasing, with more frequent epidemics and greater severity, and spread to new areas.

Nature of the infectious agent

Dengue virus is a distinct antigenic subgroup of the genus *Flavivirus*. There are four serotypes with extensive cross reactivities and strain variation. After infection, protective immunity is homotypic so that individuals can be infected simultaneously or serially by more than one serotype.

Epidemiology and geographical distribution

Reference has been made to the extensive geographical distribution of dengue throughout the tropics and warm climate regions of Africa, Asia, Australia, Oceania, India, the Caribbean Islands and the Americas. Extension to new areas is the result of uncontrolled poor housing settlements, slums and squatter camps on the peripheries of cities, resurgence of infestation with *Aedes* mosquitoes and failure of vector control. Between 2000 and 2007, more than 70 countries were affected by dengue in four continents with some five million cases reported and about 22,000 deaths.

The principal vector is *Ae. aegypti*. Other *Aedes* species of the subgenus *Stegomyia* are also implicated as vectors in Asia and in the Pacific region. Although there are many similarities with the epidemiology of yellow fever, the urban cycle involving domesticated *Aedes* mosquitoes is the most common and most important for both endemic and epidemic dengue. The incubation period is 3–14 days.

Reservoir of infection

Humans together with the mosquito.

Pathology

All four dengue virus serotypes cause three distinct syndromes: dengue fever, dengue haemorrhagic fever and dengue shock syndrome. The virus replicates in macrophages at the site of the mosquito bite, in the regional lymph nodes and subsequently the reticuloendothelial system. Viraemia is associated with circulating monocytes, and there is often severe leucopenia. A maculopapular rash on the trunk appears on day 3–5 of the illness and spreads to the face and limbs, accompanied frequently by lymphadenopathy, granulocytopenia and thrombocytopenia. Minor mucocutaneous bleeding may occur.

Dengue haemorrhagic fever is the result of increased vascular permeability, unusual bleeding manifestations, and involvement of the gut and the liver, with or without encephalopathy, and disseminated intravascular coagulation. In dengue shock syndrome, increased vascular permeability causes decreased plasma volume and clinical shock, which, if uncorrected, may lead to acidosis, hyperkalaemia and death. Most cases of dengue haemorrhagic fever and dengue shock syndrome occur in children and adolescents under the age of 15 years, with a fatality rate of 3–10%.

Dengue haemorrhagic fever and dengue shock syndrome are believed to be the result of 'immune enhancement', whereby homologous and heterologous antibodies binding to the virus, including subprotective levels of maternal dengue antibodies in infants, enhance infection of macrophages via cellular Fc receptors. Another possible explanation is that T cells exacerbate the antibody-enhanced cascade by concomitant release of cytokines by both T cells and damaged macrophages. The alternative hypothesis is that the severe complications of dengue are caused by unusually virulent strains of dengue, particularly serotype 2; however, there is no consistent relationship between strain variation and increased virulence or infectivity.

Clinical features and diagnosis

Dengue fever is characterised by sudden fever, headache, vomiting, and severe muscle and bone pain of increasing severity. The fever is biphasic, remitting on day 3–5 of the illness, followed by a maculopapular or morbilliform rash, which spreads from the trunk to the limbs and face. This second phase of the illness, which is often accompanied by recurrence of fever, is associated with lymphadenopathy, granulocytopenia and thrombocytopenia. Minor mucocutaneous bleeding may occur. The fever lasts for 3–9 days and is self-limiting.

The clinical features of dengue haemorrhagic fever are characterised by fever, rash and anorexia lasting 3–5 days, followed by hepatomegaly, hypotension and a haemorrhagic diathesis. The dengue shock syndrome is due to decreased plasma volume following increased vascular permeability, and is associated with a significant mortality of up to 10%, but which can be as high as 40–50% if untreated. Diagnosis in returning travellers may be difficult. Serological diagnosis is based on haemagglutination-inhibition and Igm antibody-capture ELISA. Definitive diagnosis is by way of virus isolation and PCR-based techniques.

Treatment is symptomatic and, in case of complications, careful management of clinical shock.

Protective measures and prevention

Live attenuated dengue vaccines are undergoing clinical trials. There is no licensed dengue vaccine. Epidemiological monitoring is important and also provides means of education and control. Vector control is essential, with the aim of eliminating the domesticated *Aedes* mosquitoes. It appears that the results of insecticide and larvicide treatment of stagnant water are temporary, and indeed re-infestations are inevitable. Nevertheless, these are essential tools for control. The traveller should employ the usual measures for the prevention of insect bites.

Japanese encephalitis, St Louis encephalitis, tick-borne encephalitis and other flavivirus infections

Introduction and definitions

The *flaviviruses* may be considered broadly in three major groups according to the associated principal clinical syndromes:

- those causing haemorrhagic fever, for example, *Yellow fever virus*
- those associated clinically with fever, rash, myalgia and arthralgia, for example *Dengue virus*
- those associated primarily with encephalitis, for example, *Japanese encephalitis virus*.

This section is devoted to the flaviviruses associated with encephalitis.

Japanese encephalitis

Japanese encephalitis virus (JEV) is the commonest cause of arboviral encephalitis in the world.

Nature of the infectious agent

JEV can be separated by nucleic acid sequencing into three genotypes with different geographical distribution. The epidemiological significance of this observation is not known. Antigenically, JEV shares some cross-reactivity with *St Louis encephalitis virus*.

Epidemiology and geographical distribution

JEV occurs in eastern, south-eastern and southern Asia, including Japan, parts of the former Soviet Union in the Far East, the Western Pacific Islands and India, where it is the major cause of viral encephalitis (Figure 7.7). The vertebrate hosts of the virus are humans and domestic animals, especially pigs, and birds, particularly water birds. The principal vector of the virus is *Culex tritaenorhynchus*, but other species of *Culex*, *Aedes*, *Anopheles* and *Mansonia* may be involved.

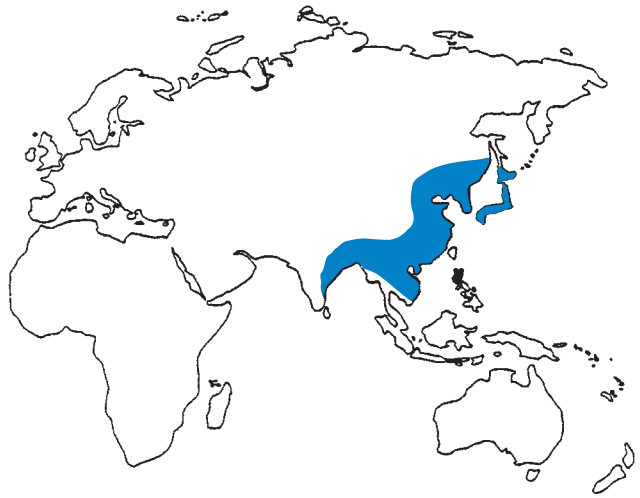

Figure 7.7 Geographical distribution of *Japanese encephalitis virus*.

Japanese encephalitis is endemic in rural areas, especially where pig farming and rice growing coexist. Epidemics occur in both rural and urban areas. The highest transmission rates occur during and immediately after the rainy season. The incubation period is 5–15 days. The virus is not transmitted from person to person. Mosquitoes remain infective for life, and pigs are a major amplifying host of the virus.

Pathology

The target cells for JEV are T cells and peripheral blood mononuclear cells. Strains of virus that invade the central nervous system cause oedema and small haemorrhages in the brain, and lesions include destruction of cerebellar Purkinje cells, neuronal degeneration and necrosis, glial nodules and perivascular inflammation. Pathological lesions in other tissues include hyperplasia of germinal centres of lymph nodes, changes in the spleen, interstitial myocarditis and focal haemorrhages in the kidney. The severity of the lesions varies considerably.

Clinical features and diagnosis

Infection may be associated with a non-specific mild febrile illness or acute meningomyeloencephalitis, occurring at rates which vary from 1 in 20 to 1 in 800 infected persons. Children are affected most commonly in endemic areas, but

infection also occurs in older age groups. Mortality rates of those with meningomyeloencephalitis is about 20% in children and up to 50% in those aged over 50 years. Permanent motor and psychological sequelae are common.

Diagnosis is based on serological assays for haemagglutination-inhibition, immunofluorescent and complement-fixing antibodies and IgM-capture ELISA.

Treatment

Treatment is symptomatic and requires excellent nursing care. Anticonvulsant treatment and management of coma may be required.

Prevention and control

Vector control is difficult and measures to prevent mosquito bites should be deployed. The most important measure of control is active immunisation of humans and domestic animals, especially pigs and horses. Immunisation is recommended for travellers to endemic areas who will be staying for a month or longer, particularly if travel will include rural areas; however, the risks to the traveller are difficult to assess except if there is a high risk of exposure, particularly towards the end of the rainy season.

St Louis encephalitis

St Louis encephalitis virus is the principal cause of viral encephalitis in the US and the outbreak in New York City in 1999 brought viral encephalitis into international prominence once again. The virus is related antigenically to the Japanese encephalitis complex of the flaviviruses. It should be noted that the virus that caused the outbreak in New York City in 1999 has now been identified as Kunjin/West Nile-like virus.

Epidemiology and geographical distribution

The virus is distributed throughout the US, and has been found in southern Canada, Central and South America and the Caribbean Islands (Figure 7.8). It is transmitted by the bite of an infected mosquito, and birds, particularly domesticated sparrows, are the principal amplifying hosts. Small mammals such as rodents and domesticated animals may also be infected; however, the virus is maintained in nature in an avian cycle and is transmitted by *Culex* mosquitoes, which feed readily on birds.

St Louis encephalitis virus is disseminated widely throughout the US and causes periodic outbreaks, usually at intervals of several years, in urban settings in California, Texas, the south-east and in the Ohio Mississippi valley.

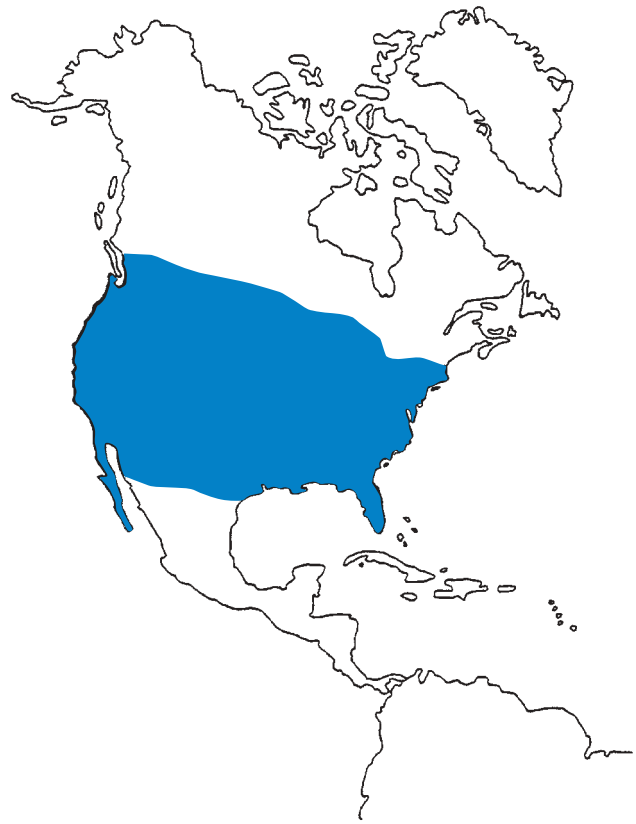

Figure 7.8 Geographical distribution of St Louis encephalitis virus.

Clinical features and diagnosis

More than 99% of infections with this virus are without symptoms. In clinical cases, the disease is characterised by fever, malaise, nausea and vomiting, and headache. Aseptic meningitis or focal encephalitis, and cranial nerve palsies in about 20% of cases, indicate involvement of the central nervous system. Coma may ensue. The case fatality rate is approximately 7% in symptomatic cases but may be higher, particularly in the elderly, when the fatality rate may be 30%.

Rapid diagnosis is based on IgM antibody capture ELISA using serum or CSF. Immunofluorescence test on cells infected with the virus is also a useful rapid diagnostic technique.

Prevention and control

A licensed vaccine is not available. The infection is controlled in the US by vector control, including water drainage and

aerial low-volume spraying of insecticides in populated areas. Secondary control measures to protect against mosquito bites should be deployed during reported outbreaks.

Chikungunya

Chikungunya virus (CHIKV) was first isolated from patients and mosquitoes in Tanzania in 1952–53 during an epidemic of dengue-like illness. CHIKV has since been found in many regions of tropical and southern Africa, and also in many parts of Asia including India, Sri Lanka, Burma, Thailand, Cambodia, Vietnam, in islands in the Indian Ocean, and more recently in Malaysia and Singapore and elsewhere, and in returning travellers. In July 2007, the first indigenous transmission of Chikungunya was reported in Italy.

CHIKV is an RNA virus belonging to the *Alphavirus* genus, transmitted by mosquitoes. The epidemiology of CHIKV infections differs. In Africa, the virus is maintained in a sylvatic cycle in savannahs and forests, but in Asia, the infection is transmitted by mosquitoes from human to human mainly in urban areas. Transmission is mainly by *Aedes aegypti* and more recently by *Ae. albopictus*, the latter being generally outdoor mosquitoes.

CHIKV causes a self-limiting non-fatal disease, severe or crippling arthralgia or arthritis, often associated with a skin rash.

Prevention relies on strict vector control and reducing mosquito-human contact. Specific antiviral drugs or licensed vaccines are not available.

Tick-borne encephalitis

Introduction and definitions

The tick-borne flaviviruses are maintained by tick–mammal cycles and by transovarian transmission in ticks. Humans are infected by virus transmitted by the bite of an infected tick or, less commonly, by drinking unpasteurised milk from infected goats or other mammals. The disease is endemic in forested parts of western, central and eastern Europe and Scandinavia, caused by *Central European encephalitis virus*, and the Far Eastern subtype or *Russian Spring–Summer encephalitis virus*.

Other viruses within the subgroup of tick-borne flaviviruses include *Omsk haemorrhagic fever virus*, *Kyasanur Forest disease virus* (India) and *Powassan virus*, which causes sporadic encephalitis in eastern parts of Canada (Ontario) and the US. These viruses are not considered further in this text.

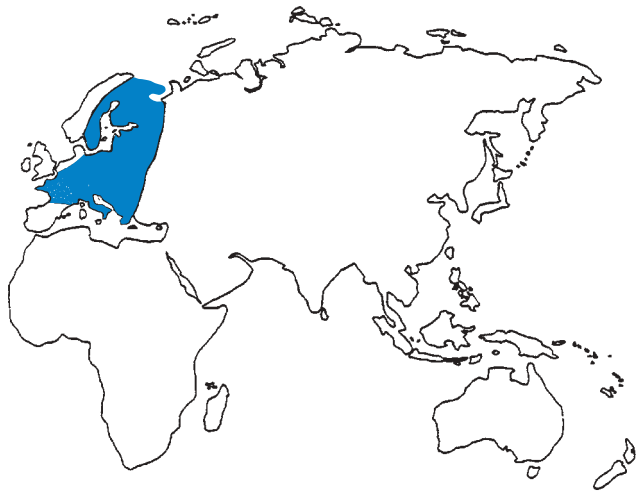

Figure 7.9 Geographical distribution of *Central European encephalitis virus*. Reproduced from Zuckerman *et al*. 2000.

Nature of the infectious agent

The tick-borne encephalitis viruses are a closely related subgroup of flaviviruses.

Epidemiology and geographical distribution

The geographical distribution of the *Central European encephalitis virus* extends to the forested areas of western, central and eastern Europe, Scandinavia, Italy, Yugoslavia and Greece, and follows closely the distribution of its arthropod vector, *Ixodes ricinus* (Figure 7.9). *Russian Spring–Summer encephalitis virus* is found in the forest belt and taiga of Russia and Siberia following the distribution of *I. persulcatus* (Figure 7.10). Infection is transmitted by the bite of an infected tick. Domestic animals, such as sheep, goats and cows, excrete virus in their milk, and ingestion of unpasteurised milk or unpasteurised milk products may transmit the infection.

The infection is endemic, with increased incidence in the summer months in relation to temperature and humidity, which affect tick activity. The infection is common in rural populations, especially in farmers and forest workers, with seroprevalence of 5–20% or even greater. The incubation period is 8–14 days.

Pathology

The virus replicates in the liver before a significant viraemia occurs. Vascular permeability is altered and the virus crosses the blood–brain barrier. Severe neuronal damage may occur,

Figure 7.10 Geographical distribution of *Russian Spring–Summer encephalitis virus*. Reproduced from Zuckerman *et al*. 2000.

affecting the cervical segments of the spinal cord, medulla, midbrain and pons. There is glial proliferation and lymphoid proliferation around vessels.

Clinical features and diagnosis

The onset of illness is sudden with a non-specific febrile illness including headache and lassitude. Visual disturbances may occur such as blurring of vision and diplopia. In the majority the illness lasts 4–7 days. A biphasic illness may follow after a short remission, with fever and signs of meningoencephalitis. Extrapyramidal and cerebellar syndromes may persist for months, and residual paralysis involving the upper limbs and the shoulder girdle is common. Mortality in different outbreaks varies from 1 to 5%.

Serological diagnosis is based on an IgM antibody-capture ELISA on serum or CSF. Haemagglutination-inhibition or neutralisation tests are useful. Virus can be isolated early after the onset of symptoms.

Prevention and protective measures

Forests in some areas of the former Soviet Union are closed to visitors.

Tick repellents are useful on outer clothes and socks, and the arms, legs and ankles must be covered. Travellers who plan to walk, camp or work in late spring and summer in the heavily forested areas listed above, especially where there is heavy undergrowth, should be immunised with a formalin-inactivated vaccine. Two doses of 0.5 ml given intramuscularly 4–12 weeks apart will provide protection for 1 year. An immunoglobulin preparation is also available for post-exposure prophylaxis.

Viral haemorrhagic fevers

Introduction and definitions

Yellow fever, which is endemic in Africa and in parts of the Americas, has a long history and is well recognised, and although it may present in severe infections as a haemorrhagic fever it is considered separately. The term 'exotic viruses' is applied to haemorrhagic viral infections that have been recognised more recently: Marburg virus disease (1967), Lassa fever (1969) and Ebola fever (1976). Two other haemorrhagic fevers are discussed in this section, Rift Valley fever and Crimean–Congo haemorrhagic fever; the former because of extensive outbreaks in parts of Africa, including the Nile delta, and the latter because of its sporadic appearance in the Middle East and Pakistan.

Natural reservoir and source

Those for *Marburg virus* and *Ebola virus* remain unknown. *Lassa virus* and other arenaviruses are normally transmitted to humans from infected rodents in Africa and South America. *Rift valley fever virus* is transmitted by mosquitoes. *Crimean–Congo haemorrhagic fever viruses*, common in Africa, Western Asia and parts of the Middle East and in Russia and Republics in the former Soviet Union, are transmitted by tick bite; human-to-human transmission has only been shown to result from contact with infected blood.

Marburg virus disease

Marburg virus disease, commonly but incorrectly named 'green monkey' disease, is a severe distinctive haemorrhagic febrile illness of humans, first described in 1967, when 31 cases with seven deaths in Germany and Yugoslavia were traced to direct contact with blood, organs or tissue cell cultures from a batch of African green monkeys (*Cercopithicus aethiops*) that had been trapped in Uganda. Several secondary cases occurred in hospital personnel by contact with the blood of patients. One further case was apparently transmitted by sexual intercourse 83 days after the initial illness, and virus was isolated from the semen. The case fatality rate was 29% for the primary cases, but no deaths occurred in the six secondary cases. This previously unrecognised disease was caused by an infectious agent probably new to medical science. Three more cases were reported in Johannesburg in 1975 in two young Australians who crossed central Africa,

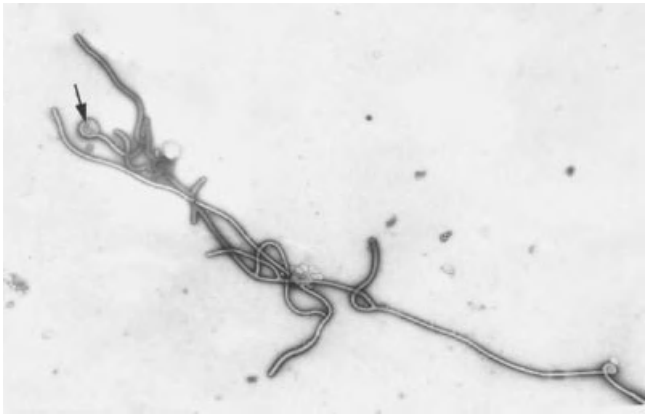

Figure 7.11 *Ebola virus* (Zaire strain). This electron micrograph illustrates a single viral particle with many branches and a torus configuration. Negative stain, ×100,000. (Courtesy of Dr David Ellis, reproduced from *Principles and Practice of Clinical Virology*, 1st edition, 1987)

and a nurse treating them. One of the primary cases died. There have been two other detected recurrences of Marburg virus disease in 1980 and in 1987, all in travellers in rural Africa, and none has led to extensive transmission.

Nature of the infectious agent

Marburg virus is classified as a filovirus with two genotypes, Marburg and Ebola. *Marburg virus* has no known subtypes and is antigenically distinct from *Ebola virus*, which has four subtypes. The morphology of these two viruses is unique with a long, but variable, filamentous shape of particles (Figure 7.11). Particles may be branched, circular, U-shaped or resemble a torus (Figure 7.12), and have a diameter of 85 nm. Spikes are present on the surface (Figure 7.12a) and there is an axial channel within the ribonucleoprotein (Figure 7.12c). The genome consists of a single negative-stranded RNA. Molecular analysis of the genome indicates

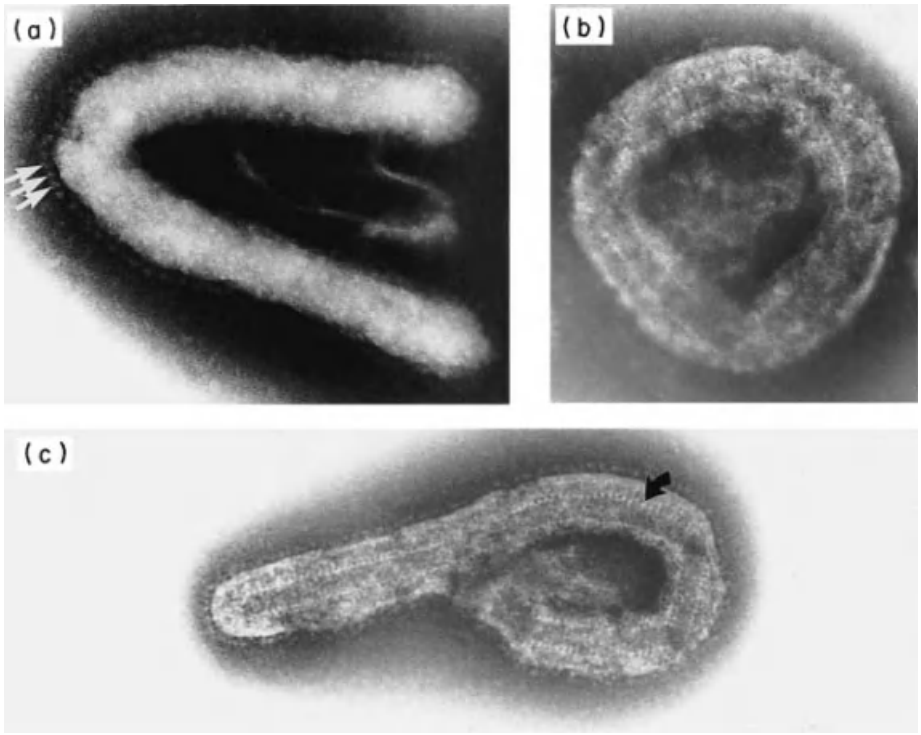

Figure 7.12 (a) Surface spikes on Marburg virus. Negative stain, ×200,000. (b) A torus form of Marburg virus showing the RNA core. Negative stain, ×200,000. (c) A filamentous form of Marburg virus curling up into a torus. The final infective particle is believed to be the torus form. ×200,000. (Courtesy of Dr David Ellis, reproduced from *Principles and Practice of Clinical Virology*, 1st edition, 1987)

that the filoviruses are the closest relatives to rhabdoviruses and paramyxoviruses.

Epidemiology and geographical distribution

The reservoir of the infection remains unknown despite intensive investigation of a host of vertebrates and anthropods. In the case of the Australian traveller who acquired the disease in Zimbabwe, he had often slept outdoors, and once in a house occupied with bats in the attic. He was also stung on the leg while resting at a roadside 6 days before the onset of illness.

The original outbreak resulting from exposure to the blood and tissues of African green monkeys remains unexplained, and since experimental infection of these monkeys invariably results in death, African green monkeys are not the natural host of the virus.

Seroprevalence studies indicate that Marburg virus disease is very rare, and the geographical distribution of primary infection appears to be limited to Central Africa. The incubation period is 4–16 days. Transmission is by contact with infected blood or tissue and transmission by the sexual route has been described.

Reservoir of the infection

Not known, although fruit bats remain prime suspects.

Pathology

There is extensive involvement of the liver, severe renal damage, changes in vascular permeability and activation of the clotting cascade, and disseminated intravascular coagulation with involvement of complex immunological mediators and cytokine release.

Clinical features and diagnosis

The illness begins characteristically with sudden onset of fever, malaise, headache and myalgia, followed by nausea, vomiting and watery diarrhoea. A maculopapular rash appears between 5 and 7 days after the onset of illness and is most marked on the buttocks, trunk and lateral aspects of the upper arms. Conjunctivitis is common. A tendency to bleed develops, particularly from the gums and from needle punctures, and severe bleeding into the gastrointestinal tract and elsewhere may occur. There is functional evidence of liver damage but clinical jaundice has not been reported. Renal damage occurs and is manifested by proteinuria, oliguria and viruria.

Laboratory diagnosis includes electron microscopy, indirect immunofluorescence, ELISA and immunoblot techniques. Antigen can be localised in tissues by immunocytochemistry and immunofluorescence, and viral RNA by PCR.

Management and treatment

Management is essentially supportive. Isolation in a Trexler tent, strict barrier nursing techniques with protective clothing by trained personnel, and careful disposal of patient material and of the deceased are absolutely essential. Laboratory procedures must be carried out in high security level 4 containment facilities.

Protective measures and prevention

Epidemiological information, surveillance and health education are important. The natural reservoir of infection remains unknown and vectors have not been identified.

Ebola virus disease

Ebola virus is the second known filovirus and was first described in 1976. Between August and November 1976, outbreaks of severe and frequently fatal viral haemorrhagic fever occurred in the equatorial provinces of Sudan and Zaire, now the Democratic Republic of Congo, causing widespread international concern. Among the 70 cases in Nzara, Sudan, 33 were fatal. Of the 230 members of the staff in the Maridi hospital, 76 were infected and 41 died. Of the 237 infected persons in Zaire, 211 died. In all, 602 persons were known to have been infected, with an overall fatality rate of 88% in Zaire and 49% in the Sudan. During laboratory investigations carried out to identify the virus, a member of the laboratory staff of the Microbiological Research Establishment, Porton Down in England, contracted the disease but recovered.

Ebola virus reappeared in the Democratic Republic of Congo in 1977: one girl died and her sister had a probable related infection, from which she recovered. A small outbreak occurred in the Sudan in 1979, but the virus was not seen again in Africa until 1994. During 1994–96, five independent outbreaks were identified: Ivory Coast (1994), Democratic Republic of Congo (1995) and Gabon (1994,1995 and 1996). All the sites were in or near tropical forests.

In 1989, *Ebola virus* appeared in cynomolgus monkeys held in a primary quarantine facility in Reston, near Washington, DC. Epidemics in cynomolgus monkeys occurred in this facility and others in 1992, and in a primate unit in Italy in 1996. The virus was introduced by monkeys captured in

the Philippines. This strain of *Ebola virus* (Reston) is highly pathogenic for non-human primates; it did not cause disease in humans in the US or the Philippines, although seroconversions have been detected in several persons in both countries.

There are at least four genetic subtypes of *Ebola virus*: Zaire (EBO-Z), Côte d'Ivoire (EBO-CI), Sudan (EBO-S) and Reston (EBO-R). Human disease has been associated only with EBO-Z, EBO-CI and EBO-S in West and Central Africa (and a laboratory-acquired infection in the UK). The geographical distribution of *Ebola virus*, based on serological surveys, suggests that it may be present in parts of Asia other than the Philippines and Madagascar.

The source of the virus is not known; however, transmission cycles of the African strains of *Ebola virus* are closely related to the rain forests, although human cases have also occurred in the forest savannas in the Sudan and Uganda. Nosocomial infections in the medical setting are important, and the epidemic in the city of Kikwit in the Democratic Republic of Congo in 1995, a town of 200,000 people, presented an enormous problem.

The Kikwit outbreak received considerable public attention. A small cluster of cases occurred among the nursing staff of a maternity hospital but was misdiagnosed as epidemic dysentery. Towards the end of the month a similar cluster was identified in the general hospital among the operating staff after a laparotomy on a laboratory technician with suspected typhoid-related abdominal perforation. A viral haemorrhagic fever was diagnosed a few days later. A total of 315 cases were identified, with a case fatality of 81%. The surviving members of 27 households where infection had occurred were interviewed; 16% of 173 household contacts of primary cases developed the infection and all had direct physical contact with the ill person or his or her body fluids. An additional risk was touching a cadaver. The international investigation team concluded that the use of barrier precautions by household members and standard strict universal precautions in hospitals would have prevented the majority of infections, and the introduction of these precautions and other public health measures coincided with the termination of the outbreak. Serological studies indicated a very low rate of subclinical transmission during the outbreak, but it was interesting that there was a significant seroprevalence among the residents of Kikwit and the surrounding villages, thought to represent temporally distant infections.

Experimental prophylaxis and treatment

Convalescent serum has not provided protection by passive transfer of putative antibodies; however, hyperimmune anti-Ebola serum produced in horses protected non-human primates (baboons) challenged experimentally with *Ebola virus*. Experimental filovirus vaccines are under development. Human monoclonal antibodies against *Ebola virus* surface protein have been produced from mRNA obtained from bone marrow of survivors. These antibodies may be useful therapeutically. Antiviral drugs are also under development. Carbocyclic 3-deazaadenosine has been shown to cure animals infected experimentally with otherwise lethal *Ebola virus* infection. Several nucleoside analogue inhibitors of *S*-adenosylhomocysteine hydrolase, an important target for antiviral activity as shown by inhibition of replication of EBO-Z *in vitro*, are being explored.

Protective measures and prevention

Although the viral haemorrhagic fevers do not, in general, pose a common hazard to travellers, the incident of the tourist in Zimbabwe in 1975 is notable. The hospital environment at times of outbreaks of infection is a risk to healthcare personnel and to patients, particularly when universal precautions for contact with blood are not in place and when syringes and needles are not sterilised or are used for more than one patient. Treatment of travellers in hospitals without the highest standards is best avoided at times of outbreaks. Travellers to endemic areas are well advised to carry approved sterile packs containing disposable syringes and needles.

Surveillance and the introduction of strict public health measures, as outlined above, are essential, and the provision of epidemiological information to travel health databases is important. Since the natural reservoir and vectors of filovirus infection are unknown, sensible precautions are important and include avoidance of quarters infested with bats and vermin, contact with dead animals, particularly chimpanzees, sleeping 'rough' or in the open, and so on.

Lassa fever and arenavirus infections

Introduction and definitions

In 1969, two missionary nurses in Lassa, in north-east Nigeria, died from a mysterious illness, and a third nurse, who was gravely ill, was evacuated by air for treatment in the US. This nurse recovered and convalescent plasma from her was used for the treatment of a laboratory worker in the US who acquired the infection while working with tissue cultures infected with blood from these patients.

Lassa fever received considerable public attention because of the high mortality, which was reported initially among

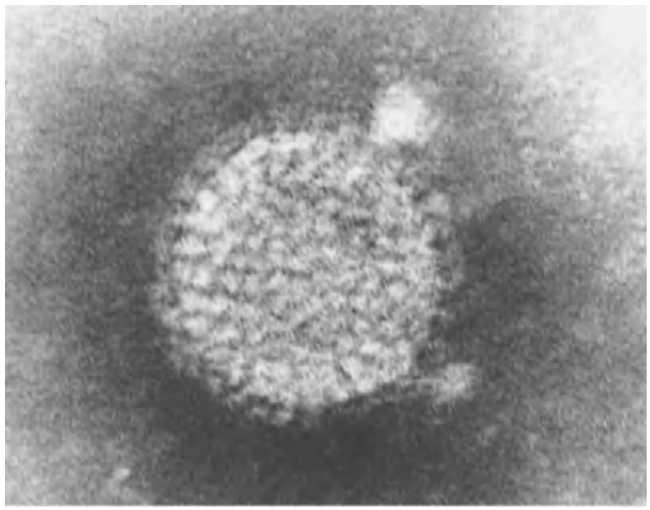

Figure 7.13 Lassa fever virus showing the characteristic sandy grain appearance and surface projections. Negative stain, ×240,000. (Courtesy of Dr David Ellis, reproduced from *Principles and Practice of Clinical Virology*, 1st edition, 1987)

expatriate medical staff and among patients admitted to hospital (20–75%) in West Africa, and the death of Dr Jeannette Troup, who first drew attention to the condition and who contracted the infection after carrying out two autopsies while investigating this fever. The virus (Figure 7.13) was isolated and Lassa fever was established as a virus disease of humans.

Nature of the infectious agent

Lassa virus is a member of the family *Arenaviridae*, genus *Arenavirus*, and is a pleomorphic enveloped single-stranded RNA particle, usually spherical, varying in size between 80 and 150 nm. The surface is covered by an array of spikes and the virus contains a large number of 20–25 nm granules, believed to be ribosomes of the host cell (Figure 7.13) acquired during the budding of the nucleocapsid from the plasmalemma. Mature infective particles are liberated by budding without destruction of the infected cell. Similar related viruses, grouped together as Mopeia strains, have been found in various areas across Africa from Zaire to Mozambique; some may yet prove to be pathogenic to humans, or may perhaps be useful as a basis for a vaccine.

The genus *Arenavirus* also includes *Lymphocytic choriomeningitis virus*, the *Tacaribe complex viruses* (haemorrhagic fever viruses of South America: *Machupo* and *Junin viruses*) as well as *Lassa virus*, all of which cross-react antigenically. Acute haemorrhagic disease due to *Machupo* and *Junin viruses* represent serious public health problems in Bolivia and Argentina respectively, and *Guanarito virus* causes Venezuelan haemorrhagic fever. The fifth member of the arenaviruses that causes infection in humans, *Lymphocytic choriomeningitis virus*, is distributed worldwide except in Australia.

The natural reservoir hosts of the arenaviruses are rodents, and these viruses are found predominantly within two families: *Muridae* (for example, mice and rats) and *Cricetidae* (for example, voles, lemmings and gerbils). The natural host of *Lassa virus* is the multimamate rat (*Mastomys natalensis*), which, in common with the host of *Lymphocytic Choriomeningitis virus*, is found in human dwellings and food stores, and is a member of the *Muridae*. In contrast, all the arenaviruses isolated from South America (with the exception of the *Tacaribe virus*, which was originally isolated from the fruit bat in Trinidad) are associated with cricetid rodents, which are found in open grasslands and forests. Human infection is usually due to contact with rodent excreta, particularly urine, which contaminate food, water and the environment.

Epidemiology and geographical distribution

Outbreaks of Lassa fever have occurred in hospitals in Nigeria and Liberia, but an epidemic in Sierra Leone in 1972 occurred in the community. Sporadic cases and outbreaks have been reported from West Africa since the original description of the disease. Many of the outbreaks have been in hospitals, with a high mortality in primary cases reaching 40–45%, but prolonged community outbreaks have also been reported. It should be noted that eight patients were evacuated to Europe or North America, but only one was flown out with full isolation precautions, and the remainder, of whom five were infectious, travelled on scheduled flights as fare-paying passengers. No secondary contact cases resulted.

Mastomys rats are infected at birth and completely asymptomatic persistent infection results. The virus is excreted in urine and other body fluids throughout the life of the rat. Seroconversion rates in the native human population are very high, indicating that the infection is common and usually asymptomatic or mild in endemic areas. Secondary spread occurs from person to person in conditions of overcrowding and in rural hospitals. Medical and nursing attendants or relatives who provide direct personal care are most likely to be infected, with high mortality rates in expatriate staff.

The incubation period is 3–16 days. Contact with contaminated material, aerosol and respiratory spread, and cuts and abrasions of the skin are likely portals of infection.

Pathology

The reticuloendothelial system appears to be the major site of viral replication before viraemia. The degree of involvement of organs varies. The major pathogenic pathways appear, in general, to be haemorrhage and an increase in vascular permeability, caused by thrombocytopenia, coagulation defects, varying degrees of disseminated intravascular coagulation resulting from activation of the intrinsic coagulation system, and vasculopathy.

Histologically, the liver is the principal target organ in human Lassa fever virus infection. The degree of inflammatory cell infiltration is slight and is unrelated to the extent of hepatocellular damage. Eosinophilic necroses are scattered throughout the lobules. Coalescence of necrotic foci, which bridge portal-to-portal and portal-to-perivenular areas of the lobule, is a usual feature. Where the damage is more extensive, large portions of individual lobules may be destroyed, but even in these areas the reticulin framework of the liver remains intact. The non-zonal distribution of necrosis distinguishes Lassa fever virus hepatitis from the classic lesion of yellow fever. At necropsy, the extent of necrosis in the liver has been sufficient to implicate liver failure as a major cause of death. Dehydration and haemoconcentration, shock syndrome, haemorrhagic manifestations and cardiovascular collapse herald death.

Clinical features and diagnosis

The spectrum of Lassa fever ranges from asymptomatic infection to a fulminating fatal disease. In children the illness is relatively mild.

The onset of illness is usually insidious, with non-specific febrile features and a sore throat and vomiting. The symptoms suddenly worsen between the third and sixth day of illness, with a high fever and severe prostration out of proportion to the degree of pyrexia. Clinical findings include conjunctivitis, severe pharyngitis and tonsillitis with whitish exudative lesions and small vesicular lesions and ulcerations, lymphadenopathy, occasionally a faint maculopapular rash and later haemorrhagic manifestations. Jaundice has not been reported, although extensive involvement of the liver is a frequent finding. Death is due to shock, anoxia, and respiratory and cardiac failure. The differential diagnosis includes malaria, typhoid, yellow fever, influenza and measles.

Laboratory diagnosis is undertaken in maximum security laboratories (category 4) by virus isolation, specific antigen detection by ELISA, specific immunofluorescent staining of acetone-fixed cells, identification of surface glycoproteins and viral neutralisation assays.

Management and treatment

Supportive measures and passive administration of immune plasma have been successful, but not always. Intravenous administration of the antiviral drug ribavirin, particularly during the early phase of the illness, has reduced mortality very significantly.

Protective measures and prevention

These are essentially as those described above for the other viral haemorrhagic fevers.

Haemorrhagic fevers of South America

These are described briefly as they do not generally present a hazard to travellers.

Argentine haemorrhagic fever is caused by *Junin virus*, first isolated in 1958. The virus causes annual outbreaks of severe illness in between 100 and 3,500 cases in agricultural workers in the wet pampas, with mortality ranging from 3 to 15% or more. Outbreaks coincide with the maize harvest between April and July, when the rodent populations reach a peak.

Bolivian haemorrhagic fever is caused by *Machupo* virus, with localised epidemics, which have waned considerably since the 1970s; human infections are now rare. Control of *Machupo*-infected rodents in households, reducing the opportunity for human contact with contaminated food and soil, accounts for the reduction of reported human infections.

Rift Valley fever

Rift Valley fever virus is a member of the family *Bunyaviridae*, genus *Phlebovirus*, and causes an enzootic infection of sheep, cattle, camels and goats in Africa and Madagascar. The virus (Figure 7.14) is transmitted by mosquitoes and the disease is characterised by necrotic hepatitis and a haemorrhagic state, although infections are frequently inapparent or mild. Humans become infected from contact with blood and tissues of domestic livestock or mosquito bite, and the infection is a mild to severe febrile illness with encephalitis, involvement of the eye, and/or haemorrhagic fever in about 1% of cases. Human cases are usually restricted to veterinary surgeons, butchers and others in close contact with the blood of domestic livestock, and there is a potential risk with ritual slaughter.

Specific tests are undertaken in maximum security laboratories and include serology, virus isolation and inoculation

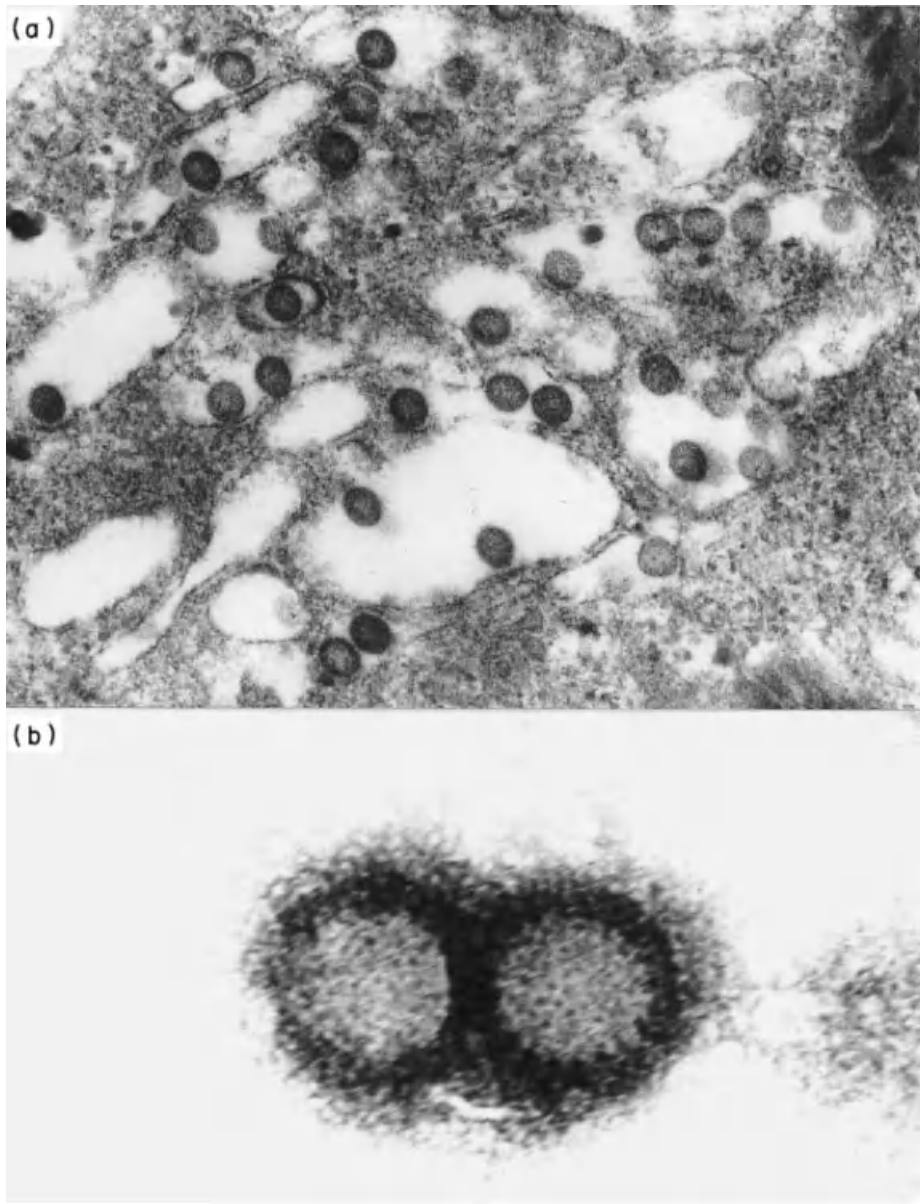

Figure 7.14 (a) Rift Valley fever virus maturing within host cell vacuoles. ×37,500. (b) Negatively stained Rift Valley fever virus particles from a patient's serum during the 1977 outbreak in Egypt. ×225,000. (Courtesy of Dr David Ellis, reproduced from *Principles and Practice of Clinical Virology*, 1st edition, 1987)

of susceptible mice. There is no specific treatment and management is symptomatic.

Prevention and control is based on avoiding contact between a susceptible human or animal and the source of virus, either the infected arthropod or vertebrate. A human formalin-inactivated Rift Valley fever vaccine has been produced in primary green monkey cells and diploid fetal rhesus lung cells for use by veterinary officers, laboratory workers, military personnel and others at risk. When given in three doses it was immunogenic in more than 95% of recipients, and Rift Valley fever infection has not been reported in vaccinated persons.

Inactivated tissue culture veterinary vaccines are available for immunisation of sheep and cattle. A live attenuated

veterinary vaccine has been developed but it is not recommended for use in unaffected enzootic zones.

Crimean–Congo haemorrhagic fever

A tick-borne haemorrhagic disease was described at the end of World War II in southern Russia and became known as Crimean haemorrhagic fever. Similar diseases were subsequently found in Africa, Pakistan and the Middle East.

Crimean–Congo haemorrhagic fever virus is a member of the family *Bunyaviridae*, genus *Nairovirus*; like *Rift Valley fever virus*, it is a single-stranded RNA enveloped particle, with an overall diameter of 115–125 nm, which includes a covering of prominent hollow surface spikes that pass out through the viral membrane.

It seems probable that animals such as domestic goats and cattle, together with their ticks, may be a reservoir, particularly in the Middle East, and that humans are infected by contact with these ticks. Infections have also been acquired by staff from contact with the blood of patients in hospitals in Pakistan, Baghdad and Dubai, and there is evidence that infection acquired in this way may carry higher mortality, increasing from 20 to 70%.

The incubation period is about 7 days, followed by a sudden fever, with nausea and vomiting. Like the other haemorrhagic viruses described above, it can cause very extensive bleeding around the mouth, teeth and nose, and may sometimes mimic an acute surgical emergency. These, and other severe haemorrhages that can occur into the skin of the upper parts of the body, appear during the following week, when the patient suffers from thrombocytopenia, a reduced white cell count and widespread impairment of liver function, without evidence of any cellular inflammation. There may also be neurological complications. Diagnosis may be confirmed by fluorescence antibody techniques and by direct examination electron microscopy of serum or by infection of suckling mice or BHK cells. Specific treatment is not yet available.

Dugbe, *Ganjam*, *Hazara* and *Nairobi sheep disease viruses*, the other members of the genus *Nairovirus*, have all been reported as having caused human infections, although none has proved fatal. There is some evidence of cross-protection among the group.

References

1. MMWR (1999) Compendium of animal rabies control. *MMWR Morb Mortal Wkly Rep* **48** (RR–3): 1–9.
2. Advisory Committee on Immunization Practices (ACIP) (1999) Human rabies prevention: United States. *MMWR Morb Mortal Wkly Rep* **48** (RR–2): 1–23.

Further reading

Hepatitis A

Catton MG and Locarnini SA (2005) Epidemiology of hepatitis A. In: Thomas HC *et al.* (eds) *Viral Hepatitis*, 3rd edn, pp. 92–108. Blackwell, Oxford.

Koff RS (1998) Hepatitis A. *Lancet* **351**: 1643–1649.

Steffen R and Gyurech D (1994) Advances in hepatitis A prevention in travellers. *J Med Virol* **44**: 460–462.

Hepatitis B

Chang M-H *et al.* (1997) Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* **336**: 1855–1859.

Harrison TJ *et al.* (2008) Hepatitis viruses. In: Zuckerman AJ *et al.* (eds) *Principles and Practice of Clinical Virology*, 6th edn, pp. 273–320. Wiley, Chichester.

Van Damme P *et al.* (1997) Integration of hepatitis B vaccination into national immunisation programmes. *Br Med J* **314**: 1033–1036.

Wright TL and Lau JYN (1993) Clinical aspects of hepatitis B virus infection. *Lancet* **342**: 1340–1344.

Tabor E (2006) Infections by hepatitis B surface antigen mutants in Europe and North America. *J Med Virol* **78**: S43–S47.

Zuckerman JN (2006) Vaccination against hepatitis A and B: developments, deployment and delusions. *Curr Opin Infect Dis* **19**: 456–459.

Zuckerman AJ and Zuckerman JN (1999) Molecular epidemiology of hepatitis B virus mutants. *J Med Virol* **58**: 193–195.

Hepatitis C

Alter MJ (1997) The epidemiology of acute and chronic hepatitis C. *Clin Liver Dis* **1**: 559–568.

MMWR (1998) Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR Morb Mortal Wkly Rep* **47**(Suppl.): 1–39.

Muerhoff SA and Dawson GJ (2004) Hepatitis C virus. In: Mushahwar K (ed.) *Viral Hepatitis*. Perspectives in Medical Virology, No. 10, pp. 127–172. Elsevier, Amsterdam.

Hepatitis D

Rosina F and Rizetto M (2005) Hepatitis D virus. Epidemiology and natural history. In: Thomas HC *et al.* (eds) *Viral Hepatitis*, 3rd edn, pp. 583–592. Blackwell, Oxford.

Hepatitis E

Mushahwar IK and Dawson GJ (1997) Hepatitis E virus: epidemiology, molecular biology and diagnosis. In: Harrison TJ and Zuckerman AJ (eds) *The Molecular Medicine of Viral Hepatitis*, pp. 33–43. Wiley, Chichester.

Panda SK *et al.* (2007) Hepatitis E virus. *Rev Med Virol* **17**: 151–180.

Human immunodeficiency virus and AIDS

Armstrong D and Cohen J (eds) (1999) *Infectious Diseases*, vol. 2, sect. 5. Mosby, London, pp. 1–28.6.

Coffin JM (1996) HIV population dynamics in vivo: implications for genetic variation, pathogenesis and therapy. *Science* **271**: 1582–1586.

Starkie J and Dale R (1988) *Understanding AIDS*. Consumers Association and Hodder and Stoughton, London.

Weiss RA *et al.* (2000) Human retroviruses. In: Zuckerman AJ *et al.* (eds) *Principles and Practice of Clinical Virology*, 4th edn, pp. 659–693. Wiley, Chichester.

UNAIDS and WHO (1988) Report on the Global HIV/AIDS Epidemic. UNAIDS and WHO, Geneva.

Viral gastroenteritis

Anderson EJ (2008) Rotavirus vaccines: viral shedding and risk of transmission. *Lancet Infect Dis* **8**: 642–649.

Desselberger U (1998) Viral gastroenteritis. *Curr Opin Infect Dis* **11**: 565–575.

Desselberger U and Gray J (2008) Rotaviruses and other viruses associated with acute diarrhoeal disease. In: Zuckerman AJ *et al.* (eds) *Principles and Practice of Clinical Virology*, 6th edn, pp. 337–373. Wiley, Chichester.

Polyomyelitis and other enterovirus infections

Fine PEM and Griffiths UK (2007) Global poliomyelitis eradication: status and implications. *Lancet* **369**: 1321–1322.

Minor PD and Muir P (2008) Enteroviruses. In: Zuckerman AJ *et al.* (eds) *Principles and Practice of Clinical Virology*, 6th edn, pp. 601–627. Wiley, Chichester.

Salisbury D and Ramsay M (2006) *Immunisation Against Infectious Diseases*, 3rd edn. Stationery Office, London.

Influenza

Anon (2005) Avian influenza A (H5N1) infection in humans. WHO Consultation. *N Engl J Med* **353**: 1374–1385.

Cox N and Subbarao K (1999) Influenza. *Lancet* **354**: 1277–1282.

Influenza A (H1N1) Virus Investigation Team (2009) Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* **360**: 2605–2615.

Watts G (2009) A/H1N1 influenza virus. The basics. *Br Med J*: **339**, 368–369.

SARS

Centers for Disease Control and Prevention (2005) Severe Acute Respiratory Syndrome (SARS), Version 2, pp. 1–10. And Supplement E: Managing International Travel-Related Transmission Risk of SARS. 20 July 2004, Version 3.

Peiris JSM and Poon LLM (2008) Coronaviruses and toroviruse. In: Zuckerman AJ *et al.* (eds) *Principles and Practice of Clinical Virology*, 6th edn, pp. 511–533. Wiley, Chichester.

Genital herpes

Corey L and Spear P (1986) Infections with herpes simplex virus, Part I and II. *N Engl J Med* **314**: 686–691, 794–757.

Whitley RJ (1996) Herpes simplex viruses. In: Field BN *et al.* (eds) *Field's Virology*, 3rd edn, pp. 2297–2342. Raven Press, New York.

Rabies

Nicholson KG (2000) Rabies. In: Zuckerman AJ *et al.* (eds) *Principles and Practice of Clinical Virology*, 4th edn, pp. 583–618. Wiley, Chichester.

WHO (1992) Expert Committee on Rabies. 8th report, World Health Organ Tech Rep Ser: 824.

Yellow fever

Centers for Disease Control (1990) Yellow fever vaccine: recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Morb. Mortal Wkly Rep* **39**: 1–6.

Schoub BD and Backburn NK (2009) Flaviviruses. In: Zuckerman AJ *et al.* (eds) *Principles and Practice of Clinical Virology*, 6th edn, pp. 669–698. Wiley, Chichester.

Stephenson JR (1988) Flavivirus vaccines. *Vaccine* **6**: 471–482.

Zuckerman AJ (1970) Yellow fever. In: Zuckerman AJ (ed.) *Virus Diseases of the Liver*, pp. 110–119. Butterworths, London.

Dengue fever

Schoub BD and Venter M (2008) Flaviviruses. In: Zuckerman AJ *et al.* (eds) *Principles and Practice of Clinical Virology*, 6th edn, pp. 669–698. Wiley, Chichester.

Teixeira MG and Barreto M (2009) Diagnosis and management of dengue. *Br Med J* **339**: 1189–1193.

Japanese encephalitis, St Louis encephalitis, tick-borne encephalitis and other flavivirus infections

Ng L-C *et al.* (2009) Entomologic and virologic investigation of Chikungunya in Singapore. *Emerg Infect Dis* **15**: 1243–1249.

Salisbury DM and Ramsay M (2006) *Immunisation Against Infectious Disease*. Stationery Office, London.

Viral haemorrhagic fevers

Fisher-Hoch SP (2008) Filoviruses. In: Zuckerman AJ *et al.* (eds) *Principles and Practice of Clinical Virology*, 6th edn, pp. 755–776. Wiley, Chichester.

Howard CR (2008) Arenaviruses. In: Zuckerman AJ *et al.* (eds) *Principles and Practice of Clinical Virology*, 6th edn, pp. 733–754. Wiley, Chichester.

Peters CJ and LeDuck J (1999) Ebola: the virus and the disease. *J Infect Dis* **179** (Suppl. 1): S1–S288.

Chapter 8 Bacterial infections in travellers

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Introduction

Most practitioners take it for granted that the earlier in the course of a bacterial infection antibacterials are given, the more rapid and certain the patient's recovery. In some conditions, such as leptospirosis and typhoid fever, there is good evidence to support this belief. As the most rapid bacteriological confirmation of diagnosis may take 24 hours, a period during which a bacterial population could double in size through as many as 60 generations, it follows that 'therapeutic trials' are good practice in managing patients with acute febrile illness if a bacterial cause is reasonably likely, provided that appropriate samples for laboratory investigations have been taken first, particularly so in the case of those returning from the tropics, in whom a firm diagnosis may not be possible before convalescence. Investigations should always include blood films for malarial parasites in patients returned from tropical countries, while prudent immediate treatment might include antimalarial therapy in addition to antibacterials that are chosen with a view to covering at least the most rapidly progressive of likely bacterial infections.

The clinical history is crucial to diagnosis and management and will establish not only where a returned traveller has been, but exactly when (knowledge of incubation periods being invaluable in establishing a differential diagnosis when this includes infections unlikely to be acquired at home), together with answers to specific enquiries into the traveller's activities abroad, including sexual activity, walking or working in scrub, any exposure of skin to water in which rats might have urinated, and any ingestion of unpasteurised milk products. Information on immunisation status is generally less important, since the efficacy of bacterial vaccines other than diphtheria and tetanus toxoid is significantly less than 100%. Travellers may be at increased risk of bacterial infections also prevalent in the UK, depending on the time or circumstances of travel, for example meningococcal infection acquired from the sub-Saharan African 'meningitis belt' during the dry season or from the annual Hajj pilgrimage to Mecca. Sexually transmitted diseases apart, travellers to temperate areas are at particular risk of only one bacterial infection – legionellosis. Although largely a disease of temperate climates, this must also be considered in those returning from the tropics who have 'stopped-over' in air-conditioned hotels on the way back.

One bacterial infection, tuberculosis, will not be considered further in this chapter because travel is of little diagnostic relevance, although it is certainly of great epidemiological significance. Most cases of tuberculosis, pulmonary and extrapulmonary, in immigrants from the Indian subcontinent arise within four years either of first arrival in the UK or of returning from a visit to the subcontinent lasting several months.

Table 8.1 lists bacterial infections encountered in British returned travellers.

A note on urgent treatment

The two treatable infections most likely to cause rapidly progressive disease in travellers recently returned from the tropics are leptospirosis and falciparum malaria. In both conditions, initial diagnostic tests may be negative but treatment with doxycycline or antimalarials should not be delayed if either is possible. The finding of an eschar (which may be mistaken for an infected insect bite) in someone whose activities placed them at risk of typhus should also lead to immediate treatment with doxycycline, although imported typhus fevers are rarely life threatening.

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Table 8.1 Bacterial infections in British returned travellers

Infection[a]	Most common features	Incubation (days)	Most rapid diagnosis
Legionellosis (100)	Pneumonia	2–10	Urinary antigen; serology
Typhoid (400)	British Asians visiting Indian subcontinent. Fever usually sustained	7–21	Blood culture
Typhus (10)	Walking in scrub in Africa or Southeast Asia; eschar	Scrub 10–21 Tick 5–7	Serology
Leptospirosis (10)	Exposure to rat-infested water; multisystem; leucocytosis in 80%	4–19	Serology
Brucellosis (10)	Ingestion of unpasteurised milk products	5–30	Blood culture
Diphtheria (<1)	Membranous tonsillitis in non-immune travellers. Indian subcontinent most common source of British imports	5–9	Culture of throat swab = carriage. Membrane + bull neck + toxicity = diphtheria
Endemic relapsing fever (<1)	Exposed to risk of tick bites; relapsing fever	5–15	Blood film
Melioidosis (1)	Pneumonia; septicaemia	2–21 (chronic cases may present years after infection)	Culture of blood, sputum or other samples
Lyme disease (5–10)	Erythema migrans; arthritis or central nervous system involvement	21 (mean)	Clinical diagnosis; Serology

[a]Values in parentheses are the number of cases currently identified in average years in England and Wales.

Legionellosis

Definition

Infection with *Legionella pneumophila* may result in one of two distinct diseases: Pontiac fever, a mild non-focal infection with an incubation period of 1–2 days; and Legionnaires' disease, characterised by pneumonia, with multisystem disease in severe cases, which has an incubation period of between 2 and 10 days, with a median of 6 days.

Nature of the infectious agent

L. pneumophila is a Gram-negative, strictly aerobic bacillus that stains poorly or not at all with standard methods and will not grow on usual bacteriological media. These unusual features explain why it remained unrecognised as a human pathogen until the exceptionally thorough investigation of an outbreak of pneumonia in Philadelphia in 1976.

Epidemiology

L. pneumophila is a saprophyte found in still water, where it lives in biofilms in conjunction with a number of other organisms, including environmental amoebae. For it to pose a threat to human health it must be present in significant numbers, which is only likely with water temperatures of greater than 20°C, and it must be aerosolised in order that it can be inhaled. Power station cooling towers have given rise to outbreaks, but in travellers the major risk appears to be from hotel air conditioning and showers. If plumbing complies with agreed standards then the risk is greatly reduced, but this is frequently not the case. Up to 50% of cases of Legionnaires' disease reported in the UK are associated with travel abroad: European data from 2007 demonstrate that four countries, Italy, France, Spain and Turkey, were associated with approximately 60% of travel-associated cases, with smaller number of cases acquiring infection in Thailand, the USA, Tunisia and other European countries [1]. Increasing numbers of cases are being reported in travellers to countries outside Europe, and this is likely to continue as the proportion of elderly travellers to these countries also continues to increase.

Reservoir of infection

See Epidemiology. Infection invariably results from inhalation of bacteria in aerosolised water. Human-to-human transmission has never been described.

Pathology

In most cases of Legionnaires' disease pathological changes are confined to the lung and consist of an acute inflammatory exudate into the alveoli. In severe cases inflammation is

generalised and both lungs are involved, but more often part of a single lobe bears the brunt. Panlobar pneumonia is unusual. Organisms are usually found within macrophages in the alveoli but not the bronchi. In severe cases there may be generalised pulmonary oedema and the systemic changes of septic shock.

Clinical features

Case history 1

A 42-year-old smoker presented 4 days after returning from a one-week holiday in Turkey. He complained of headaches and feverishness, but said his cough was 'no worse than usual'. Clinical examination was normal, other than a temperature of 39°C. Chest X-ray (CXR): hazy patch left hilum. Outcome: recovered on clarithromycin therapy. *L. pneumophila* infection was subsequently confirmed serologically. Enquiries revealed that his 62-year-old father-in-law had been on holiday with him and was at home with 'flu. He was also treated for legionellosis and the diagnosis was subsequently confirmed in him as well.

Legionnaires' disease typically begins as a 'flu-like illness, that is, with aches and pains, headache and malaise. In many cases the pneumonic element remains clinically inapparent and any returned traveller exhibiting these symptoms requires a chest X-ray urgently as it may provide a clue to the diagnosis, which would justify immediate administration of appropriate treatment, usually a macrolide antibacterial agent. Most patients have a dry cough but this may not be very noticeable and can be overlooked. Mucopurulent sputum may be produced after 2 to 3 days of dry cough. The clinician may be put off the diagnostic scent by systemic symptoms such as vomiting, diarrhoea, confusion and delirium, especially in the elderly. Chest radiographs typically show one or more patchy infiltrates, usually involving only one lung, but in severe cases areas of consolidation may be visible in both. Liver function tests characteristically show mild to moderate hepatitis with raised transaminases and slight increase in bilirubin.

Most patients improve after 2 to 3 days of appropriate therapy but in severe cases – most often in the elderly and those with pre-existing lung disease – the patient may develop respiratory failure and/or shock despite treatment and die within a few days of the onset of symptoms.

The diagnosis must be founded on clinical suspicion, as it will not be made from the result of any routine test such as blood culture. The detection of antigen in the urine is the most rapid non-invasive test currently available, giving a positive result within a few days of admission to hospital in 80% of patients with *L. pneumophila* serogroup 1 infection, which causes over 80% of human disease [2]. Direct immunofluorescence of bronchoalveolar washings obtained at bronchoscopy provides the diagnosis in about 50% of cases ultimately proved by culture of sputum in special media containing charcoal, yeast extract, L-cysteine, ferric salts and a pH buffer. The isolation of morphologically characteristic Gram-negative rods in 2–5 days, but not on routine culture media, is presumptive evidence of legionella infection. Serological tests provide retrospective confirmation; however, it is important to recognise that serology may not become positive for 4–6 weeks after onset of symptoms, and thus an initial negative result taken during the acute phase should not be regarded as excluding legionella infection.

Treatment

Retrospective analysis of the first outbreak of Legionnaires' disease to be recognised showed that survival rates were higher in patients treated with erythromycin. Subsequently, erythromycin, administered intravenously in ill patients, has become the treatment of choice if the diagnosis of legionellosis is suspected. In severe illness rifampicin may be added, although there is limited evidence of benefit.

More recently, some of the newer macrolides such as azithromycin have been demonstrated to have superior *in vitro* activity against *L. pneumophila*. Fluoroquinolones also have greater *in vitro* activity and may penetrate tissue more effectively than the macrolides; early reports suggest good *in vivo* efficacy, although no prospective controlled trials have been performed (reviewed by [3]).

Prevention

There is no vaccine for legionellosis. Enforcement of building regulations to minimise stagnation of warm water that will subsequently be released into the atmosphere substantially reduces the risk of the disease.

In travellers, even a provisional diagnosis of Legionnaires' disease should cause clinicians to enquire about travelling companions who have been exposed to the same environment, in whom immediate treatment at the onset of symptoms would be indicated.

Typhoid and paratyphoid fever

Definition

Systemic infections spread by the faecal–oral route. Unlike the zoonotic salmonellae that cause enteritis, *Salmonella*

typhi and *paratyphi* infection is confined to humans and is acquired either from cases or carriers.

Nature of the infectious agent

S. typhi are Gram-negative bacilli that possess flagellae, do not ferment lactose in most cases, but do produce hydrogen sulphide from sulphur-containing amino acids.

Epidemiology

The survival of the typhoidal salmonella depends ultimately on deficient sanitation, which ensures transmission to susceptible individuals via food or water that has been contaminated by the faeces or urine of a case or carrier. Cases are infectious from the first week of illness, and in most cases bacilli are excreted throughout the remaining illness and for about 1 month thereafter. About 10% of cases excrete bacilli for a further 2 months, while about 2% become permanent carriers. This is most likely in individuals with pre-existing gall bladder disease, but *S. typhi* may give rise to a low-grade cholecystitis *de novo*. Coexisting *Schistosoma haematobium* infection of the bladder predisposes to chronic urinary excretion.

In 2006/7, more than 90% of cases in the UK occurred in travellers returning from the Indian subcontinent, particularly in individuals travelling to this area to visit friends and relatives. This group is less likely than other groups of travellers to seek pre-travel advice and vaccination, and it is important to raise awareness of the risk of acquiring enteric fever in travellers and health professionals.

Pathology

S. typhi and *paratyphi* typically penetrate the mucosa of the small intestine without giving rise to enterocolitis, but in a minority of cases of typhoid fever there is a history of watery diarrhoea within one to two days of the likely time of ingestion of the organism. The bacilli multiply within mononuclear cells in small intestine-associated lymphoid tissue, then pass via lymphatics to continue intracellular multiplication in liver, spleen and bone marrow. About ten days after ingestion (the incubation period being inversely related to the infecting dose), bacteria enter the bloodstream and symptoms occur. In untreated individuals, inflammation and necrosis continue in lymphoid tissue in the small bowel mucosa until there is considerable mucosal destruction, with resultant intestinal haemorrhage or perforation, typically in the third or fourth weeks of infection.

Clinical features

Case history 2

A 33-year-old woman was admitted with a 5-day history of fever and headache, which began 2 days before she left India, where she had been visiting relatives for 5 weeks. Her temperature was 39°C but examination was otherwise normal and she did not appear ill. A chest film was clear and no malarial parasites were seen on blood films. The next day Gram-negative bacilli were seen in blood cultures taken on admission and she was prescribed intravenous ceftriaxone. The bacilli were identified as *S. typhi* the next day. She remained pyrexial for 5 days but was otherwise well and she made an uncomplicated recovery.

The illness begins insidiously, after an incubation period of between 1 and 3 weeks, with malaise, fever and headache. In most cases the fever gradually increases through the first week and the patient is rarely afebrile. Children, however, often have a swinging fever. At the end of the first week bloodborne spread of the organism may lead to focal symptoms such as cough (and chest X-ray may show areas of consolidation), meningism (occasionally with lymphocytes in cerebrospinal fluid, CSF), constipation or watery diarrhoea (it is as much a myth that diarrhoea is not a feature of typhoid fever as it is that it is usual). Most travellers returning to western countries seek medical advice within a week of onset of fever and therefore the presentation of typhoid fever seen in western Europe and North America is that of a comparatively mild 'flu-like illness with a persistent fever. Provided blood cultures are taken at this point – when the patient is not clinically septicaemic – the diagnosis can be made and the patient treated before becoming significantly ill. By the second and third week of untreated illness the abdomen is likely to become tender and distended, and tends to be silent. The liver and spleen are palpably enlarged in at least half of the cases. By the third week of untreated illness, complications are likely, the most important being overwhelming septicaemia, severe focal infection such as meningitis or pneumonia, and necrosis of the lymphoid follicles (Peyer's patches) of the small intestine, leading to ulceration with potentially massive bleeding or perforation. Untreated, mortality from typhoid fever is about 20%, even in previously healthy individuals.

Diagnosis

A 'flu-like illness with documented fever in an individual who has returned from an insanitary region in the previous

month should lead to consideration of the diagnosis. Blood cultures should be taken and *S. typhi* will grow in 70–80% of cases in standard media within 2 days. Cultures of bone marrow aspirate have an even higher yield. In a minority of cases cultures remain negative, and a therapeutic trial of an antibacterial agent is justifiable under circumstances that make the diagnosis likely, provided the practitioner bears in mind that the fever typically takes between 3 and 7 days to settle, even when the strain is fully sensitive to the agent used. *S. typhi* serology is unreliable and now rarely used.

Treatment

Until recently the fluoroquinolones were regarded as first-line therapy for enteric fever, but uncontrolled use of this group of antibiotics, particularly in the Indian subcontinent, has resulted in emergence of strains with decreased susceptibility, and these agents can now no longer be used as empirical therapy for enteric fever [4]. Intravenous ceftriaxone is effective, and a high proportion of strains isolated in the UK also show susceptibility to oral azithromycin. Fluoroquinolones are associated with the lowest risk of relapse and should be used for susceptible strains. Treatment should be given for 14 days to minimise the risk of relapse.

Typhus fevers

Introduction

Imported typhus fevers are generally mild and self-limiting zoonoses that are seen exclusively in travellers who venture on foot into bush and scrub (Table 8.2).

Nature of the infectious agent

Rickettsiae are small pleomorphic bacteria that are obligate intracellular parasites and therefore do not grow on standard bacteriological media. Their inability to survive outside the cytoplasm of their host cell results from their dependence on the host for ATP. Outside the host cell they rapidly lose energy and, as a result, their infectivity.

Epidemiology

The rickettsiae that cause disease in travellers are zoonoses in the ecology of which humans play an accidental and incidental role, unlike louse-borne typhus, which causes epidemics when people crowd together in refugee camps. Infections in travellers are sporadic and are largely confined to those who wander in woods in North America, bush in Africa and scrub in Southeast Asia. (In Central and North America domestic dogs may act as a reservoir for Rocky Mountain spotted fever [RMSF] rickettsiae so that, in theory, dog ticks could bite people in their homes and thus transmit infection indoors.)

Tick typhus is regularly seen by practitioners working in southern Africa in people who walk in game reserves and similar terrain, and is seen increasingly in tourists on safaris, particularly those who do walking safaris. Scrub typhus is found in pockets through much of Southeast Asia and causes sporadic illness in the native population engaged in slash-and-burn subsistence farming. It is comparatively common in the Sylhet region of Bangladesh, the origin of Britain's earliest Indian restauranteurs. On returning to their ethnic homeland, they may help their relatives and become infected in the process.

Table 8.2 Rickettsial infection in travellers

Disease (symptoms)	Organism	Geographic distribution	Vector (from rodent reservoir)	Clinical
Rocky Mountain spotted fever	*Rickettsia rickettsii*	June to September in USA (principally eastern) and Canada, Central America	Tick	Prominent rash
Mediterranean spotted fever (boutonneuse fever, tick typhus, South African tick bite fever)	*R. conorii; R. africae*	Mediterranean coast, Black Sea basin, eastern, central and southern Africa	Tick	Eschar usual
Scrub typhus (tsutsugamushi fever)	*R. tsutsugamushi*	Southwest Pacific, Southeast Asia, Japan	Mite	Eschar usual

Pathology

The intracellular multiplication of rickettsiae gives rise to a diffuse lymphocytic vasculitis with endothelial damage. Increased permeability and foci of haemorrhage are the result. Platelet aggregation at sites of vascular injury commonly gives rise to thrombocytopenia, but full-scale disseminated intravascular coagulation is rare in the non-epidemic typhus fevers.

Clinical features

Scrub and tick typhus

Case history 3

A 24-year-old female backpacker presented on her return from a 4-week visit to Thailand with a 'flu-like illness associated with macular rash. On examination, there was an eschar on her upper arm, with regional lymphadenopathy. She was treated with oral doxycycline and made a good recovery. The diagnosis of scrub typhus was subsequently confirmed serologically.

Headache, myalgia and feverishness – a nondescript 'flu-like illness – are the first, and often the only, symptoms of tick and scrub typhus, and typically start quite abruptly between 5 and 7 days after the arthropod bite. Examination will reveal an eschar at the site of a tick bite in most cases. This typically has a black necrotic centre, resembling a black scab, up to 1 cm in diameter surrounded by an area of acute inflammation about 3 cm across. It is often dismissed as a secondarily infected insect bite. A dull maculopapular rash, usually involving palms and soles, appears about 5 days after the onset of illness. Cough with radiographic evidence of a patchy pneumonitis is common in scrub typhus. Untreated, symptoms usually settle spontaneously after about 10 days, but with appropriate treatment recovery is usually apparent after 2 days.

Rocky Mountain spotted fever

The illness ranges from a mild 'flu-like illness to the picture of overwhelming sepsis with multiorgan failure and a generalised maculopapular rash, which typically appears on the third day. Purpura are common and the picture then resembles meningococcaemia, except that in the latter condition the purpuric rash typically appears within hours of the onset of symptoms and a maculopapular element is absent. The incubation period ranges from 2 to 10 days but as the ticks responsible for transmission are tiny, and their bites are seldom noticed, this is usually of little help in establishing the diagnosis in endemic areas. Outside these, the fact of having walked or camped in rural North America, especially in the Carolinas, Virginia, Maryland, Georgia, Tennessee and Oklahoma between June and September, is enough to justify empirical treatment in an individual who is ill with compatible symptoms (reviewed in [5]).

Diagnosis

Empirical therapy of patients ill with suspected rickettsioses is vital because there is currently no reliable early diagnostic test. In practice, patients with 'flu-like symptoms, a normal white cell count and thrombocytopenia in some cases, are likely to receive antimalarials if they have travelled in a malarious area, but such patients should always be inspected carefully for an eschar and, if a compatible lesion is seen, they should also be treated for possible typhus. The diagnosis can be confirmed later by a rise in antibody titre.

Treatment

Tetracyclines have been used most extensively in rickettsial infection and remain the treatment of choice. Doxycycline 100 mg daily is effective in tick and scrub typhus, whereas double this dose is advised in Rocky Mountain spotted fever. As with most infections, there is no good evidence on optimal duration of treatment: continuing for 2 days after defervescence is conventional.

Prevention

When walking in endemic areas, travellers should try to minimise pushing through dense vegetation and stay in relatively open areas as far as possible. Inspecting the body for ticks every few hours, and removing them by steady traction, will help to protect travellers, but the best, ultimate protection is the preparedness of physicians to administer tetracyclines promptly on the first reasonable suspicion of rickettsial infection.

Leptospirosis

Definition

A spirochaetal infection, the severity of which ranges from inapparent to a life-threatening illness with multisystem involvement. Infection is usually acquired as a result of exposure to fresh water contaminated with the urine of domestic or wild animals.

Epidemiology

A zoonosis with a worldwide distribution, the polar regions excepted. Infected reservoir animals excrete spirochaetes in their urine and humans are infected either by direct exposure (chiefly in farm workers, for example in milking parlours in the case of serovar Hardjo) or via contact with contaminated water during activities such as wading through streams or in paddy fields or while washing, etc. Leptospires gain entry via a cut or skin abrasion or mucous membrane. Travellers engaging in adventure water sports such as rafting, kayaking and canoeing, and military personnel training in the tropics are at particular risk (reviewed in [6]). The contact may not, however, have been obvious to the subject (*see* Case history 4). The incubation period is about 10 days, with a range of between 4 and 19 days.

Case history 4

A 46-year-old man was admitted with 'flu-like symptoms 4 days after returning from staying with relatives in Jamaica. On admission, he was pyrexial, jaundiced and had photophobia but no neck stiffness. There was no rash. Immediate investigations revealed a neutrophil count of 17×10^9 per litre and evidence of a mild hepatitis. Despite immediate commencement of penicillin, he developed anuric renal failure and required dialysis for 3 weeks before complete recovery. Leptospirosis was diagnosed serologically during convalescence. He recalled seeing rats around the 'outside privy' and said he had worn sandals throughout his visit.

Reservoir of infection

Serovars pathogenic to humans are harboured by domestic animals, including dogs, and livestock including cattle, pigs and horses. A variety of wild animals may harbour pathogenic serovars but rats are the most important natural reservoir.

Pathology

In severe cases with multisystem involvement (Weil's disease) there is extensive vasculitis with focal haemorrhage in many organs. The kidneys are swollen, with evidence of interstitial nephritis, and there may be necrosis of proximal tubular epithelium. Spirochaetes have been seen between the necrotic cells. Meningeal involvement suggests viral meningitis, in that lymphocytes usually predominate, but a polymorphonuclear leucocytosis is usual in the blood. Multisystem infection may be immunologically mediated.

Clinical features

Most infections are subclinical but clinical illness usually consists of a 'flu-like illness with headache and muscle pain. This may progress seamlessly to a multisystem disease (*see* Case history 4) or the patient may recover before apparently relapsing with recurrence of fever, and in some cases aseptic meningitis, hepatitis, renal failure and a haemorrhagic rash.

Diagnosis

A high index of suspicion is required as the disease presents in a non-specific manner. The diagnosis can usually be made serologically, with positive results appearing from day 6 to 12 of illness; however, some patients may remain seronegative throughout if their infecting serotype is not detected by the currently available assays. Leptospires can be cultured from blood or CSF in the first few days of illness, and subsequently in urine. Culture requires specialised media and takes 5–6 weeks.

Treatment

Early treatment may be life saving. Those patients with a biphasic illness who are not treated until there is evidence of multisystem disease may show no response to antibiotics and require supportive therapy. The spirochaetes are sensitive to penicillin, tetracyclines and macrolides (e.g. erythromycin).

Prevention

Advice to travellers who intend to walk in Africa or Southeast Asia should include a caution against wading barefoot through water likely to be contaminated by rat urine, especially still or slow-flowing water close to human habitation. Doxycycline prophylaxis has been shown to be of benefit in some studies of high-risk travellers.

Brucellosis

Definition

A zoonosis transmitted to humans via contact with infected animals or by ingestion of their unpasteurised milk. Now virtually extinct as an endemic infection in Britain, it is still seen occasionally in returned travellers.

Nature of the infectious agent

The genus *Brucella* includes three species pathogenic to man: *B. melitensis* (enzootic in sheep and goats), *B. abortus* (cattle) and *B. suis* (pigs). Brucella organisms are slow-growing, Gram-negative fastidious aerobes. Growth is encouraged by vigorous aeration and many strains require supplementary carbon dioxide.

Epidemiology

The reservoirs of infection are wild and domestic animals. Cattle, pigs, sheep and goats are the main sources of human infection but related wild species are also reservoirs of the organisms. Globally, most cases arise in farmers and others whose work or way of life brings them into regular contact with reservoir animals; the occasional cases now imported to Britain are usually the result of ingestion of unpasteurised milk products. An epizootic in Arabian Gulf countries in the past two decades led to thousands of human cases in Bedouin and other indigenous people, with occasional cases in western expatriates who had received their hospitality.

Clinical features

There is a range of clinical presentations from an acute 'flu-like illness, with chills, myalgia and headache, to a more chronic disease with an insidious onset in which the fever may be low grade or intermittent and focal symptoms may eventually emerge (reviewed in [7]). Meningitis, with lymphocytes predominating in the CSF, has been comparatively common in the recent Arabian Gulf epidemic, but sacroilitis, vertebral discitis with later extension to adjacent vertebrae, and infection of the genitourinary tract are well documented, as is endocarditis. Depression is a common accompaniment to chronic infections.

Diagnosis

The organism can be isolated on culture of blood, bone marrow or other tissues: cultures are positive in the majority of individuals with acute febrile presentations, but in only a minority of those with chronic illness, and may require prolonged incubation. Serological tests are reliable if IgM is detected in acute cases, although when IgG antibody predominates it may be difficult to distinguish between active and past infection. More recently, detection by polymerase chain reaction (PCR) from blood or other samples has shown promise.

Treatment

The treatment of brucellosis requires combination therapy for protracted periods, to prevent relapse because of the intracellular persistence and low growth rate of brucellae. Combinations of doxycycline, rifampicin and an aminoglycoside have given higher treatment success rates than other combinations or monotherapy (reviewed [8]).

Diphtheria

Definition

An acute infection of tonsils and pharynx, less often of larynx or nose, or of skin. In individuals immunised against the exotoxin produced by *Corynebacterium diphtheriae*, infection may still occur but gives rise to no more than moderate inflammation of the infected site. In the unimmunised, the production of toxin leads to the characteristic leathery pharyngeal exudate, swelling of the neck, cranial and peripheral demyelinating neuropathy and myocarditis. In toxaemic cases, early administration of antitoxin is vital.

Nature of the infectious agent

C. diphtheriae is a non-sporulating pleomorphic Gram-positive bacillus. The species is subdivided into three types, *gravis*, *intermedius* and *mitis*, based on *in vitro* culture characteristics. The organisms are generally not particularly invasive, remaining in the superficial layers of pharyngeal mucosa; the major virulence determinant is the production of a potent exotoxin which inhibits protein synthesis in mammalian cells. *Gravis* biotypes are most likely to be toxigenic. Non-toxigenic strains can cause local inflammation without systemic complications.

Epidemiology

Carriage of *C. diphtheriae* and diphtheria is confined to humans. Although immunisation does not prevent acquisition and carriage of *C. diphtheriae*, and even a minor inflammatory reaction at the site of infection, clinical infection of any kind is extremely rare in immunised communities. Furthermore, clinical infection is rare even in many unimmunised communities, including most of sub-Saharan Africa, but cases are comparatively common in the Indian subcontinent, the Middle East and in the Russian Federation, especially the southern republics and in emigrants from these areas to St Petersburg and Moscow. Travel to these areas

poses a theoretical risk to older travellers in whom immunity might be waning. In the UK, diphtheria has been rare since the introduction of mass immunisation in 1942, but there are still occasional deaths, most recently in two unimmunised children, one of whom had acquired infection in an endemic area.

Toxigenic strains of *C. diphtheriae* can also cause cutaneous infection. These appear as shallow ulcers and can resemble insect bites. Although systemic upset is rarely associated with cutaneous infection, skin lesions can act as a reservoir of infection, and transmission of both cutaneous and pharyngeal disease to contacts can occur.

Clinical features

Diphtheria typically starts with a sore throat and difficulty in swallowing after an incubation period of 5–9 days. The patient appears 'toxic', is flushed, with a rapid pulse, and examination of the throat typically reveals a grey membrane adherent to the tonsils. Within a few days there may be swelling of the neck and evidence of myocarditis or peripheral neuropathy.

Diagnosis

The diagnosis is usually a presumptive one, based on the clinical features. The organism can occasionally be identified on throat swab or smears of the membrane, but definitive identification is based on culture of *C. diphtheriae* from such samples. Selective media are required for optimal growth, and thus the laboratory must be alerted if there is clinical suspicion of diphtheria.

Treatment

C. diphtheriae is sensitive to penicillins but this has no effect on toxaemia, at the first sign of which antitoxin should be administered. Evidence of disordered conduction on electrocardiogram (ECG) is enough to justify immediate administration of antitoxin, which is ineffective once the toxin has bound to target cells (reviewed in [9]).

Prevention

Travellers visiting areas where diphtheria is known to be prevalent should receive a booster of low-dose vaccine if more than 10 years have passed since a primary course. This is most important for longer-term travellers who will be living or working with the indigenous population. Antibiotic prophylaxis with erythromycin is indicated for contacts of a confirmed case.

Relapsing fever

Definition

A systemic spirochaetal disease characterised by periods of fever lasting from 2 to 10 days, separated by fever-free intervals of 2 to 4 days. The epidemic louse-borne variety, caused by *Borrelia recurrentis*, is now confined to the Horn of Africa and poses a threat to visiting healthcare and aid workers, whereas the endemic tick-borne variety, caused by at least 15 *Borrelia* species, occurs in pockets in Asia, Africa, South America and the western USA.

Nature of the infectious agent

Borreliae are microaerophilic spirochaetes that give rise to relapsing fevers because mutation of their surface antigens allows them to 'escape' from antibody produced by the host. Relapses eventually cease, but as many as 10 or more have been observed in untreated cases.

Epidemiology

For distribution, *see* Definition. Louse-borne strains of *B. recurrentis* are spread by lice from person to person, but, as human carriage has not been documented, it is possible that in some cases epidemics may originate from endemic tick-borne disease in circumstances in which lice are prevalent, i.e. where populations are displaced and crowded as a result of war or national disaster. Endemic cases are zoonoses with a reservoir in small rodents and other mammals. The vectors are soft ticks of the genus *Ornithodoros*, which also act as a reservoir because *Borrelia* are passed transovarially to the next generation. These ticks abound in dwellings with mud walls and earth floors. They feed at night, engorging rapidly before dropping off so that the host is usually unaware of having been bitten.

Pathology

Disappearance of spirochaetes from the blood coincides with a rise in temperature and pulse rate, with neutropenia and thrombocytopenia. This is thought to represent a Jarisch–Herxheimer reaction triggered by the release of cellular pyrogens. Eventual recovery is usual in endemic disease, but widespread haemorrhage in the skin and viscera is seen in fatal cases of the epidemic form.

Clinical features

After a mean incubation period of 7 days, the onset of spirochaetaemia coincides with fever, rigors, headache and

muscle pains. The subsequent relapsing pattern of disease is very characteristic (*see* Definition). Neutropenia and thrombocytopenia are usual and there may be slight elevation of liver enzymes. The diagnosis is established by seeing extracellular spirochaetes in Giemsa- or Wright-stained blood smears taken during febrile relapses.

Treatment

A single dose of a tetracycline or erythromycin is usually curative. Antibiotic treatment typically triggers a Jarish–Herxheimer reaction, with pyrexia, hypotension and leucopenia. This is thought to represent an extreme form of the febrile response associated with clearance of organisms from the bloodstream in the untreated host, and is not prevented by prior administration of steroids.

Prevention

Travellers to endemic areas should be warned of the danger of sleeping in mud huts. Those working with refugees should ensure that they remain louse-free by regular dusting of clothing with insecticides.

Melioidosis

Definition

A systemic illness caused by *Burkholderia pseudomallei* characterised by pneumonia and/or septicaemia in the acute form, and chronic lung nodules or skin disease in the chronic form. Melioidosis is endemic in residents in many parts of the world, and has been described in travellers to these areas.

Nature of the infectious agent

B. pseudomallei is a Gram-negative bipolar aerobic bacillus that can propel itself using flagellae. It produces both exo- and endotoxins, although the role of these in pathophysiology is not established. An unusual pathogen in western countries, the organism may be overlooked when grown on conventional media, and the laboratory should be alerted if melioidosis is thought to be a possible diagnosis so that cultures can be set up on selective media. Furthermore, laboratory-acquired infections have been described and appropriate infection control measures should be taken when handling samples and cultures.

Epidemiology

The organism is found in soil and water in many parts of the tropics, including Southeast Asia, India, the Middle East, Africa, and Central and South America. Most cases are reported from South East Asia and northern Australia with highest prevalence in northern Thailand. Residents in these areas are at high risk, particularly if occupationally exposed to water, for example rice paddy workers in Thailand, and seroprevalence rates of 80% have been reported in rural Thai children. A history of water contact is almost invariable: the organism enters via breaks in the skin or through mucous membranes, or may be inhaled in aerosolised water droplets. The mean incubation period is 9 days, but the organism may persist for decades as a latent infection, and so melioidosis should be considered in anyone with an unexplained suppurative infection who has spent time in an endemic area at any point in their life. In the UK, around 20 cases have been reported in the past 10 years, in travellers from Thailand, Bangladesh, Vietnam, Malaysia, India and Brazil.

Clinical features

The spectrum of disease ranges from asymptomatic/mild infection to fulminant sepsis. Individuals with concomitant

Case history 5

A 55-year-old married clerk was admitted with a history of fever, rigors, headache, rhinitis and dry cough with pleuritic chest pain commencing the day after his return from a 2-week holiday in Thailand 4 days earlier. He had no previous medical history. Examination was unremarkable. Investigations revealed slight hyponatraemia, a neutrophil leukocytosis, CRP 285, CXR showed vague homogenous shadowing in the R apex. Normal or negative: renal function, MSU, CSF, blood cultures, malaria screen, stool cultures, MRI brain, HIV screen and hepatitis A/B, legionella and dengue fever serology.

Five days after admission he needed catheterising for urinary retention, and the next day produced a somewhat purulent urethral discharge. He subsequently developed acute renal failure, probably pre-renal, his liver enzymes deteriorated and he became hypoxic. A coliform organism was isolated from blood and urine cultures and treatment was started with meropenem and clarithromycin. The organism was subsequently identified as *B. pseudomallei*. He made a full recovery on an eight week course of doxycycline and co-trimoxazole.

He probably acquired his infection while walking in rural northern Thailand. Such severe illness is unusual in previously healthy individuals. A history of diabetes, steroid therapy or alcoholism is more usual. Focal infection is commonest in the lung followed by skin and prostate.

diabetes mellitus, renal failure, alcoholism, thalassaemia or immunodeficiency are at particular risk of severe disease. Patients present with fever, and may also have symptoms and signs of focal disease, for example cough and pleuritic chest pain, abdominal symptoms or bone/joint pain. The illness then progresses rapidly to multiorgan failure and death if untreated; the mortality with antibiotic treatment still exceeds 80% in patients with bacteraemia if facilities for intensive care are not available.

Chronic infection is seen in approximately 10% of cases. The clinical picture may mimic tuberculosis, for example chronic lung nodules or pneumonia, osteomyelitis, chronic abscesses or skin lesions.

Diagnosis

The diagnosis is made by isolation of the organism from clinical samples, including blood, bone marrow, urine and throat swabs. Serology is not always available and may be difficult to interpret in endemic countries.

Treatment

Severe septicaemic cases require prolonged intravenous antibiotic therapy, for at least 2 weeks, or until defervescence occurs. Suitable agents include ceftazidime and meropenem. Intravenous therapy should then be followed by a prolonged (up to 6 months) oral course to reduce the risk of relapse of infection, using cotrimoxazole and doxycycline.

Prevention

In endemic areas, travellers should avoid exposure to water and soil, particularly if they have other health problems that predispose to severe diseases. Person-to-person spread has been described but is very rare. There is no vaccine available, and the role of post-exposure prophylaxis is uncertain.

Lyme disease

Definition

Lyme disease is a multiorgan infection caused by *Borrelia burgdorferi*, a spirochaete bacterium transmitted by *Ixodes* ticks. In Europe, two additional species are more commonly encountered: *B. afzelii* and *B. garinii*.

Epidemiology

Lyme disease was identified in 1975 as the result of investigation of a cluster of cases of juvenile arthritis, centred around the town of Lyme, Connecticut, in the USA. Since then it has been found in many parts of the USA, Europe, Russia, China, Japan and Australia. Since most patients acquire Lyme disease by walking in rural areas frequented by deer, an association with leisure, vacation and travel is not surprising and is borne out by a recent survey from a London hospital [10]. They identified 65 patients diagnosed with Lyme disease between 2002 and 2007. Almost half of the patients acquired infection in continental Europe with Germany, France, Sweden and Norway the principal sources, while 20% came from North America, principally New England. The remaining 34% were acquired in the UK. Incubation period from tick bite (when known) to first symptoms ranged from 3 to 82 days with a mean of 21.

Clinical features

Presenting features of Lyme disease range from an aymptomatic infection to significant multisystem illness, predominantly involving the nervous system and musculoskeletal system in its late stages. It is classified into three stages: early localised disease, characterised by erythema migrans lesions which may be single or multiple; early disseminated disease, in which there is systemic upset (*see* Table 8.3); and persisting late disease, with features such as arthritis, polyneuritis, encephalopathy, cranial nerve palsies and carditis.

Diagnosis

The Infectious Diseases Society of America defines a case on the basis of either (a) the presence of 'erythema migrans', an expanding, red, flat, roughly circular lesion more than 5 cm in diameter without features of cellulitis, with or without central clearing, which appeared more than 3 days after exposure to a tick or travel in an area endemic for Lyme disease, or (b) clinical features consistent with Lyme disease with an appropriate exposure history and positive Lyme serology reported by a recognised laboratory. Serology is usually negative during acute infection; PCR of blood or of biopsy from the erythema migrans lesion may be positive,

Table 8.3 Clinical features of early disseminated Lyme disease [10]

Erythema migrans	91%
Systemic symptoms (of which half were fevers)	62%
Headache	31%
Arthralgia or arthritis	28%
Radiculitis	11%
Cranial neuropathy	5%

but is not used routinely. Early antibiotic therapy may prevent an antibody response developing, so it is important to recognise that erythema migrans after either likely exposure or a definite bite is sufficient for the diagnosis. Serology has higher sensitivity in later stages of the infection, but a small proportion of patients with chronic Lyme disease may be seronegative. The internet has spawned a minor epidemic among worried well individuals with non-specific symptoms who have been persuaded that neither an absence of defining symptoms nor negative serology from a proper laboratory excludes the diagnosis. There is no rational basis for their conviction.

Treatment

For early disease, oral doxycycline for 14–21 days is recommended. Amoxycillin or cefuroxime may be used for those who are unable to take doxycycline due to adverse reactions, pregnancy or breastfeeding. For later stage disease, intravenous ceftriaxone is used for patients with central nervous system involvement, while patients with arthritis may be treated with prolonged oral therapy.

Prevention

The key preventive measure is avoidance of tick bites, by wearing protective clothing and use of repellants. Those in at-risk areas should check regularly for attached ticks with prompt removal of any found attached. Athough a vaccine against Lyme disease was licensed, it was withdrawn from use several years ago due to its adverse events profile.

Panton-Valentine leucocidin (PVL) strains of *Staphylococcus aureus*

Skin problems are frequently reported by returning travellers, and bacterial infection is a common cause. A review of 60 travellers with skin and soft tissue infections (SSTIs) treated in Paris identified *S. aureus* as the cause in 15 (43% of culture-positive cases; [11]). Of these four were PVL strains (see below) but none was resistant to methicillin. Reasons for the high prevalence of SSTIs in travellers include insect bites, which may become secondarily infected, activities that result in skin trauma and physical crowding, all of which probably explain their prevalence in military personnel.

Leucocidin-producing strains of *S. aureus* were identified a century ago when the exotoxins produced by these bacteria were characterised. They were named after Panton and Valentine in 1932 but remained a minority interest until the last decade when they were increasingly recognised as a cause of relatively severe skin lesions ranging from folliculitis to deep abscesses, of a septic state resembling meningococcemia, and of a severe pneumonia. Whether the apparent increase is real is hard to know, but there does appear to be an association with travel. One series of 13 travel-associated cases treated in Edinburgh identified both Fiji and sub-Saharan Africa as the source of several cases. Three of these isolates were methicillin-resistant [12].

Case history 6

A previously healthy 38-year-old woman developed cough, fever and haemoptysis on the flight back from a family holiday in Lanzarote. Within hours she required ventilation for respiratory failure, her chest X-ray showing bilateral patchy consolidation. Staphylococcal infection was considered at the time of presentation and her initial antibiotic regime included appropriate therapy for PVL *S. aureus* infection (see United Kingdom Health Protection Agency guidelines); a PVL strain of *S. aureus* was subsequently isolated from a blood culture. She eventually made a full recovery. Of concern is the fact that anti-staphylococcal antibiotics are not routinely included in regimens for treating severe community-acquired pneumonia and they should be considered in patients with life-threatening pneumonia, especially when it was acquired overseas.

Conclusion

Bacterial infections cause significant morbidity and mortality in travellers. Some may present in a characteristic fashion, making diagnosis straightforward if one is aware of their global distribution and clinical features, for example a patient with tick typhus presenting with a rash and eschar. However, some may mimic locally acquired infection, for example a patient with melioidosis presenting with a pneumonic illness, or brucellosis with vertebral osteomyelitis. Thus it is essential to consider whether a travel-related infection may be present in any patient presenting with acute sepsis.

Furthermore, one must also consider bacterial resistance patterns in the country of origin. Resistance rates very widely for many community-acquired bacterial infections, for example penicillin-resistant *Streptococcus pneumoniae*, fluoroquinolone-resistant *Salmonella typhi* and extended spectrum β-lactamase (ESBL)-producing Gram-negative organisms, and the dramatic increase in international travel,

with shorter travel times, has facilitated the spread of resistant organisms. Nosocomial outbreaks of multidrug resistant *Acinetobacter baumanii* have arisen through international transfer of patients between hospitals, highlighting the need for more systematic screening of patients arriving from other countries. The World Health Organization Global Strategy for Containment of Antimicrobial Resistance, published in 2001, calls on countries to develop internal systems to control antibiotic use, improve infection control and monitor antibiotic resistance. However, international collaboration is also necessary to develop and coordinate surveillance across boundaries, since it is likely that bacterial resistance will continue to increase throughout the world in future years.

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References

1. Joseph CA *et al.* (2009) Travel-associated Legionnaires' disease in Europe in 2007. *Eurosurveillance* **14**: 1–5.
2. Plouffe JF *et al.* (1995) Reevaluation of the definition of Legionnaires' disease: use of the urinary antigen assay. *Clin Infect Dis* **20**: 1286–1291.
3. Dedicoat M and Venkatesan P (1999) The treatment of Legionnaires' disease. *J Antimicrob Chemoth* **43**: 747–752.
4. Clark TW *et al.* (2010) Enteric fever in a UK regional infectious diseases unit: a 10 year retrospective review. *J Infection* **60**: 91–98.
5. Dantas-Torres F (2007) Rocky Mountain spotted fever. *Lancet Infect Dis* **7**: 724–732.
6. Pavli A and Maltezou HC (2008) Travel-acquired leptospirosis. *J Travel Med* **15**: 447–453.
7. Pappas G *et al.* (2005) Brucellosis. *New Engl J Med* **352**: 2325–2336.
8. Skalsky K *et al.* (2008) Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials. *Br Med J* **336**: 701–704.
9. Bonnet JM and Begg NT (1999) Control of diphtheria: guidance for consultants in communicable disease control. *Communicable Disease and Public Health* **2**: 242–249.
10. Dillon R *et al.* (2010) Lyme Disease in the UK: clinical and laboratory features and response to treatment. *Clin Med* **10**: 454–457.
11. Hochedez P *et al.* (2009) Skin and soft tissue infections in returning travellers. *Am J Trop Med Hyg* **80**: 431–434.
12. Helgason KO *et al.* (2008) Panton-Valentine Leukocidin-positive *Staphylococcus aureus* and foreign travel. *J Clin Microbiol* **46**: 832–833.

Chapter 9 Vector-borne parasitic diseases

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Introduction

Parasitic diseases transmitted through exposure to a particular insect vector will be discussed in this chapter. Although these infections are uncommon in travellers, their incidence is rising as more travellers engage in extreme forms of travel, particularly to remote areas where the vectors are present and inadequate preventive measures have been taken [1]. Most vector-borne parasitic diseases can be avoided if adequate protection against the vector is used.

In this chapter we shall discuss the common vector-borne parasitic diseases of humans, focusing on prevention of infection through understanding of the life cycle of the parasite and interruption of transmission. Infections of particular concern, leishmaniasis and trypanosomiasis (both African and American), will be covered in more detail. Infections that are rare in travellers but potentially serious, including filariasis and babesiosis, will be discussed briefly.

We have also included a section on schistosomiasis, an extremely important parasitic disease that is not classically vector-borne. Malaria, the most important and deadly of the vector-borne parasitic diseases, is covered in Chapter 10 and will not be discussed here.

True vector-borne parasitic diseases

Leishmaniasis

Leishmaniasis is the third most common parasitic disease in the tropics. There are estimated to be in excess of 1.5 million infections annually worldwide, of which 90% occur in just seven endemic countries [2]. The parasite is transmitted to humans through the bite of the phlebotomine sandfly and causes a spectrum of clinical disease. Chronic disease is caused by the obligate intracellular amastigote stage of the parasite.

The *Leishmania* parasite is a flagellate protozoan from the class Kinetoplastidea, which also includes the genus *Trypanosoma*, which will be discussed later in this chapter.

Leishmania produces a range of clinical syndromes, depending on the infecting species.

- Old World cutaneous: *L. tropica*; *L. major*; *L. aethiopica* (Mediterranean, Middle East, Asia, Africa).
- New World cutaneous: *L. mexicana* complex; *L. Viannia* subgenus (Central and South America).
- Mucosal: *L. Viannia* subgenus, including *L. V. braziliensis* (Central and South America).
- Visceral (VL) sometimes known as Kala-azar: *L. donovani* complex (Mediterranean, Indian Subcontinent, South America).

Differentiation between the infecting species is important, as *Leishmania Viannia* can cause metastatic destructive mucosal disease after the primary lesion has resolved and requires intravenous rather than local or oral treatment.

Parasite life cycle

The vector of the Leishmania parasite is the phlebotomine sandfly (genus *Phlebotomus* and *Lutzomyia*), of which there are 30 species worldwide recognised to transmit the parasite. Transmission occurs through bites to the skin, but VL has also been reported rarely through needle sharing and from mother to baby [3, 4]. There is a risk, albeit very small, of VL transmission through blood transfusion in endemic areas.

The reservoir of infection is in wild or domestic mammals. Humans can act as reservoir hosts for VL due to *L. donovani* and for *L. tropica*.

The female sandfly bites during the cooler times of dusk and at night. Each blood meal enables maturation of a batch of eggs, which are then scattered in the breeding site. Different subspecies are distributed throughout the tropics

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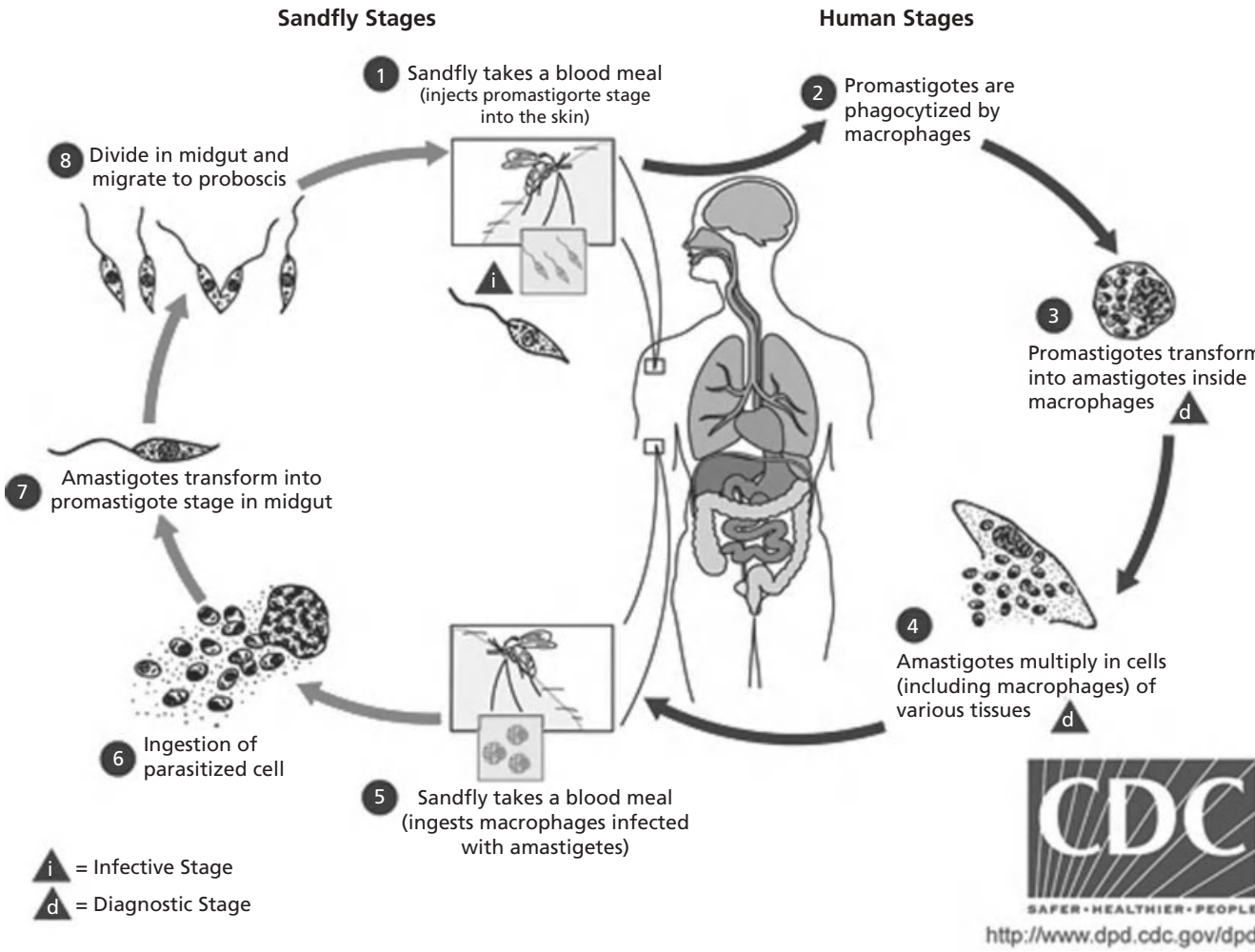

Figure 9.1 Life cycle of the Leishmania parasite. Used with permission from the Centers for Disease Control and Prevention.

and subtropics. Sandflies living in the distribution of Old World disease classically are found in dry rural areas, such as beaches, river beds, rocky mountains and valleys [5]. However, sandflies in central and south America are found in tropical forests and, increasingly, urban areas [6, 7]. The parasite undergoes maturation and division in the gut of the sandfly to transform from amastigotes to infective promastigotes. These are transmitted to the host via the next bite for a blood meal. Breeding sites for the sandfly are very hard to identify, leading to extreme difficulty in controlling the infection via vector control programmes. The life cycle of the parasite is shown in Figure 9.1.

Epidemiology

Leishmaniasis is endemic in the following areas: Mediterranean basin, Near East, Middle East, Indian subcontinent, China, North Africa, Ethiopia, Central and South America [8]. Cutaneous leishmaniasis is seen in Europe, mainly in travellers, military personnel and migrants from endemic areas. With the ongoing deployment of troops to conflicts and military exercises in *Leishmania*-endemic areas, the incidence of leishmaniasis in soldiers is increasing, and should be included in the differential diagnosis of all non-healing skin lesions in that group [9–11].

The incidence of Old World leishmaniasis is directly related to the length of exposure. Therefore expatriates living in rural areas in endemic countries are at higher risk than casual tourists, due to the time-dependent risk of sandfly bites. Old World leishmaniasis is increasingly being recognised in British tourists and expatriates in Mediterranean Europe, particularly southern Spain, where a predominately elderly population is resident in dry and semi-rural areas [10, 12].

Figure 9.2 Distribution of leishmaniasis. Essential Leishmaniasis Maps, http://www.who.int/leishmaniasis/leishmaniasis_maps/en/, used with permsision from WHO.

The risk of New World leishmaniasis is highest among rural travellers and military personnel, particularly on forest explorations in tropical rainforest areas. Travellers, particularly backpackers, are at risk of New World leishmaniasis during adventure jungle travel in Central and South America [12, 13].

Individuals with lymphocyte depletion or dysfunction, particularly those with human immunodeficiency virus (HIV) infection, or receiving chemotherapy or monoclonal antibody therapy, are at particular risk of VL. These individuals should be advised to avoid travel to endemic areas. If travel is necessary, then strict adherence to bite prevention should be employed as treatment of the immune-compromised patient with VL presents particular clinical challenges, and the parasite can be very difficult to eradicate.

Diagnosis

The most common clinical manifestation of leishmaniasis is a cutaneous ulcer, of which there are estimated to be in excess of 1.5 million cases annually worldwide [8]. Leishmaniasis should be considered in the differential diagnosis of all non-healing skin lesions in travellers from endemic areas (*see* Figure 9.2). Cutaneous leishmaniasis presents as skin lesions that develop weeks or months after infection.

Traditionally, the diagnosis of cutaneous leishmaniasis has been made on a combination of clinical suspicion and biopsy of the lesion for microscopy, histology and culture. Diagnostic testing has more recently been supplemented very successfully with molecular diagnostics. Polymerase chain reaction (PCR) has been shown to improve sensitivity, and is able to differentiate between species of *Leishmania*, an

important determinant of treatment choice. PCR sensitivity for the diagnosis of cutaneous leishmaniasis has been reported as 95–99%. PCR also has the advantage of being feasible on paraffin-embedded histology specimens, facilitating diagnosis in specimens transported to the reference laboratory [14].

The incubation period of VL may vary between 2 weeks and 18 months and may be asymptomatic or present as an acute, sub-acute or chronic illness. Diagnosis can be made by microscopy, culture or through serological testing using indirect immunofluorescent antibody test (IFAT), enzyme-linked immunosorbent assay (ELISA) or direct agglutination test (DAT).

Treatment

All cases of leishmaniasis should be managed after discussion with a centre with specialist expertise in infectious diseases and/or tropical medicine.

Old World cutaneous leishmaniasis (OWCL) with a small number of lesions may be managed with intralesional sodium stibogluconate [15] and response rates to this treatment are excellent. The lesion may also regress and heal spontaneously if left untreated over several months to a few years, depending on the infecting species.

New World cutaneous leishmaniasis (NWCL) due to *L. Viannia* is treated with intravenous sodium stibogluconate. Intralesional therapy is not appropriate as there is a significant relapse rate (1–5%) even with intravenous therapy [13]. Relapses are associated with destructive nasal lesions, which may progress rapidly if untreated. All patients should be warned about relapse and advised to re-present if the lesion recurs, or they develop ENT symptoms such as nosebleeds or nasal stuffiness. Advanced mucosal leishmaniasis may become permanently disfiguring.

VL may be treated with one of the following agents, depending on funding, availability and host suitability:

- liposomal amphotericin B
- sodium stibogluconate
- paromomycin
- miltefosine.

All cases should be discussed with, and ideally referred for management in, a specialist centre.

Control

Due to the differing and complex nature of sandfly habitats and poor understanding of their resting places, vector control methods have met with varied success [16]. Methods employed to date have included indoor residual spraying and destruction of sandfly breeding sites where they can be identified. Case finding and treatment are used where humans are reservoir hosts. Culling of wild/stray dogs has been of limited value.

Prevention

As vector control programmes have poor success rates, prevention of leishmaniasis is mainly through bite avoidance. There is no drug prophylaxis.

Travellers to rural areas that are known to be endemic should wear protective clothing, particularly if trekking in forests or mountains, or on military deployment. Clothing worn should ideally have been impregnated with an insecticide such as permethrin. The application of DEET to the skin and use of impregnated bed-nets where available are also important measures to prevent bites. There is no difference in the preventive methods between NWCL and OWCL.

Acquisition of OWCL by tourists and expatriates in the Mediterranean basin is rare but increasing. Millions of people travel to southern Europe for annual holidays, but very few become infected. These travellers do not classically seek pre-travel advice and there is very little publicity about the risks of leishmaniasis from cheap short-haul travel to southern Europe. As there is very little awareness of the risk from sandfly bites, bite avoidance is more difficult, as beachwear and lightweight holiday clothes are often worn and insect repellents are rarely used. Where relevant travellers, particularly those at risk (see above), should be advised of the risk of leishmaniasis in the area they propose to visit.

Trypanosomiasis

Trypanosomiasis is caused by the protozoan parasite *Trypanosoma*. The disease exists in two very different forms, confined to distinct geographical regions with their own associated vectors. Each will be discussed separately with reference to acquisition and modes of prevention by travellers.

African trypanosomiasis (sleeping sickness)

African trypanosomiasis is caused in West and Central Africa by *Trypanosoma brucei gambiense*, and in East and Southern Africa by *T .brucei rhodesiense*. The vector of both is the tsetse fly genus *Glossina* (*G. palpalis* and *G. tachinoides* in West Africa and *G. morsitans*, *G. swynnertoni* and *G. pallidipes* in East Africa). Their geographical distribution overlaps in Central Africa, notably in Uganda, where both diseases have been described. Detailed information is available via the WHO website at http://www.who.int/trypanosomiasis_african/country/foci_AFRO/en/index.html

West African trypanosomiasis

Sixty million people are thought to be at risk, with 30,000 estimated cases annually [17, 18], but due to difficulties in diagnosis and case finding, the precise number is unknown. The infection occurs predominately in rural areas where pastoral care of cattle and fishing are the main means of income. It is rare in travellers, with fewer than 50 cases reported in the literature in the past 10 years.

About 4 to 14 days after the infected tsetse fly bite an oedematous swelling know as a chancre may develop at that site. This is rare in gambiense infection and the first sign of illness is usually fever, with other non-specific features such as headache and joint pains (Stage I, haemolymphatic stage). Enlarged lymph nodes are found in the posterior triangle of the neck (Winterbottom's sign).

After several months the disease progresses to Stage II (meningoencephalitic stage), characterised by headache, lethargy, confusion, day–night reversal and somnolence. Without treatment the infection is universally fatal.

East African trypanosomiasis

T.b. rhodesiense causes a much more acute illness than *T.b. gambiense*, and is much more common in travellers, due to the number of tsetse flies in the great nature reserves of East and Southern Africa, and the associated number of visitors to this region [19, 20]. A chancre is much more commonly seen and the symptoms of Stage I disease are very severe. Death may occur at this stage due to acute myocarditis [21]. The disease may progress to Stage II in a matter of weeks.

Parasite life cycle

The main reservoir of West African trypanosomiasis is in humans, whereas that of the East African form is wild animals such as bushbuck, and domestic livestock. The habitat of the tsetse fly (palpalis group) is the banks of rivers and lakes in wooded areas. The habitats of the morsitans group of tsetse flies are more open wooded areas and savannah plains. Both types bring the fly into contact with humans sharing their habitat for different reasons. Both sexes of the tsetse fly feed exclusively on blood meals from the reservoir host.

West African and East African tsetse flies are physically indistinguishable to the non-expert eye. Tsetse flies are relatively easy to recognise due to the presence of the characteristic 'hatchet cell' in the wing and the large prominent proboscis.

The parasite life cycle is summarised in Figure 9.3.

Epidemiology

Humans are the main reservoir of *T.b. gambiense* and are most commonly bitten by the riverine tsetse fly when fishing or using water at river edges for drinking or washing. Travellers very rarely come into prolonged contact with this environment and therefore West African trypanosomiasis is very rare in that group. As *T.b. rhodesiense* is carried by flies that inhabit open savannah areas more travellers are exposed to this infection through visiting popular large animal game parks in East Africa.

Diagnosis

Stage I disease: trypanosomes can be visualised on a Giemsa-stained blood film. In travellers, the diagnosis is sometimes made when the film is sent for malaria parasites and trypanosomes are seen instead. A blood sample in EDTA can also be spun down and parasites visualised in the buffy coat. Trypanosomes may also be detected in stained smears of material aspirated from lymph nodes. Serology is helpful in the diagnosis of West African trypanosomiasis but of virtually no value in Stage I East African disease.

Stage II disease: diagnosis is based on cerebrospinal fluid (CSF) examination for evidence of pleocytosis, trypanosomes and antitrypanosomal antibodies.

Before lumbar puncture is attempted a negative blood film for trypanosomes is a pre-requisite due to the theoretical risk of introduction of trypanosomes from the blood to the CSF [22].

Any case of African trypanosomiasis in returning travellers should be referred to a specialist centre without delay.

Treatment

West African trypanosomiasis

Stage I is treated with eflornithine or suramin or pentamidine. Stage II is treated with eflornithine, which supercedes melarsoprol. Nifurtimox-eflornithine combination therapy has recently been introduced as a replacement for melarsoprol.

East African trypanosomiasis

Stage I is treated with suramin. Stage II is treated with melarsoprol.

Control

Tsetse flies are strongly attracted to the colour blue. This has led to limited but good quality control methods in parts of

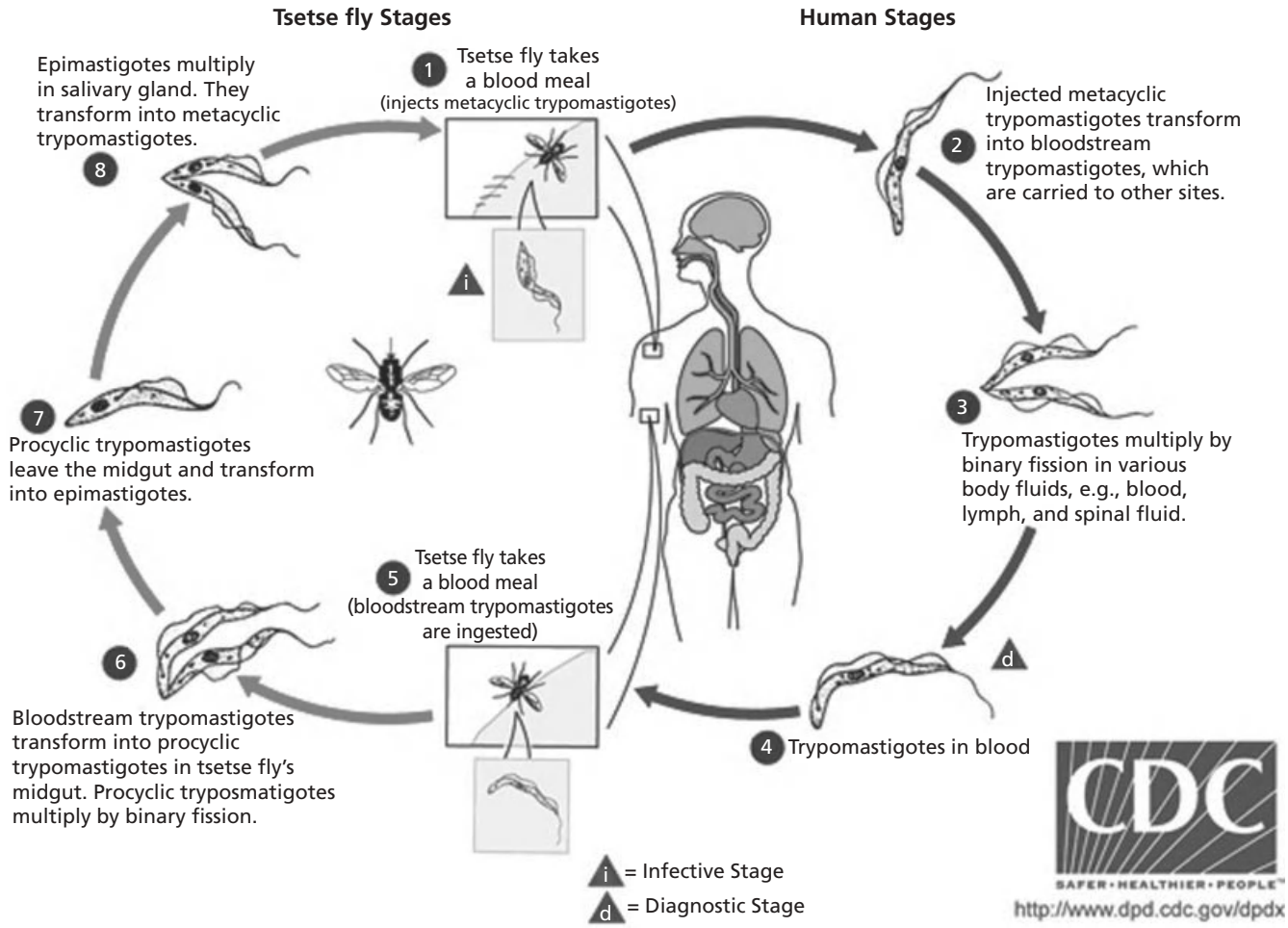

Figure 9.3 Life cycle of *Trypanosoma brucei*. Used with permission from the Centers for Disease Control and Prevention.

Eastern and Southern Africa where the morsitans group has a significant economic impact, causing epidemics in domestic cattle. Blue-coloured insecticide impregnated sheets are made into traps which attract the fly and cause death after contact with the sheet. The traps usually move with the direction of the wind to attract the fly through movement. Mass treatment of cattle has also been postulated to control infection. Traps have had less effect with controlling the riverine tsetse fly, and control is more complex in West Africa [23].

Prevention

Control in endemic areas is based on case finding and treatment of infected individuals, plus the use of tsetse fly traps.

Prevention of African trypanosomiasis by travellers is through bite avoidance. The tsetse fly is a daytime feeder and will bite through clothes. It is particularly attracted to the colour blue (which is used in traps) and is susceptible to permethrin. It will follow cars believing them to be cattle, and therefore open-top safari vehicles are a significant risk. Bite risk can be minimised by wearing thick permethrin-impregnated clothing, and avoiding areas where cattle and buffalo are present. Any suspected fly should be killed to avoid biting. The bite is characteristically painful and induces a large, tender swelling. If bitten, travellers should be aware of the risk of trypanosomiasis and report any non-healing bite sites with necrotic areas, febrile illness or lymphadenopathy to a doctor when possible. Travellers should enquire locally if there is a tsetse fly control programme in the area they are visiting, as these have met with great success in some areas.

There is no vaccine against human African trypanosomiasis and no suitable chemoprophylaxis.

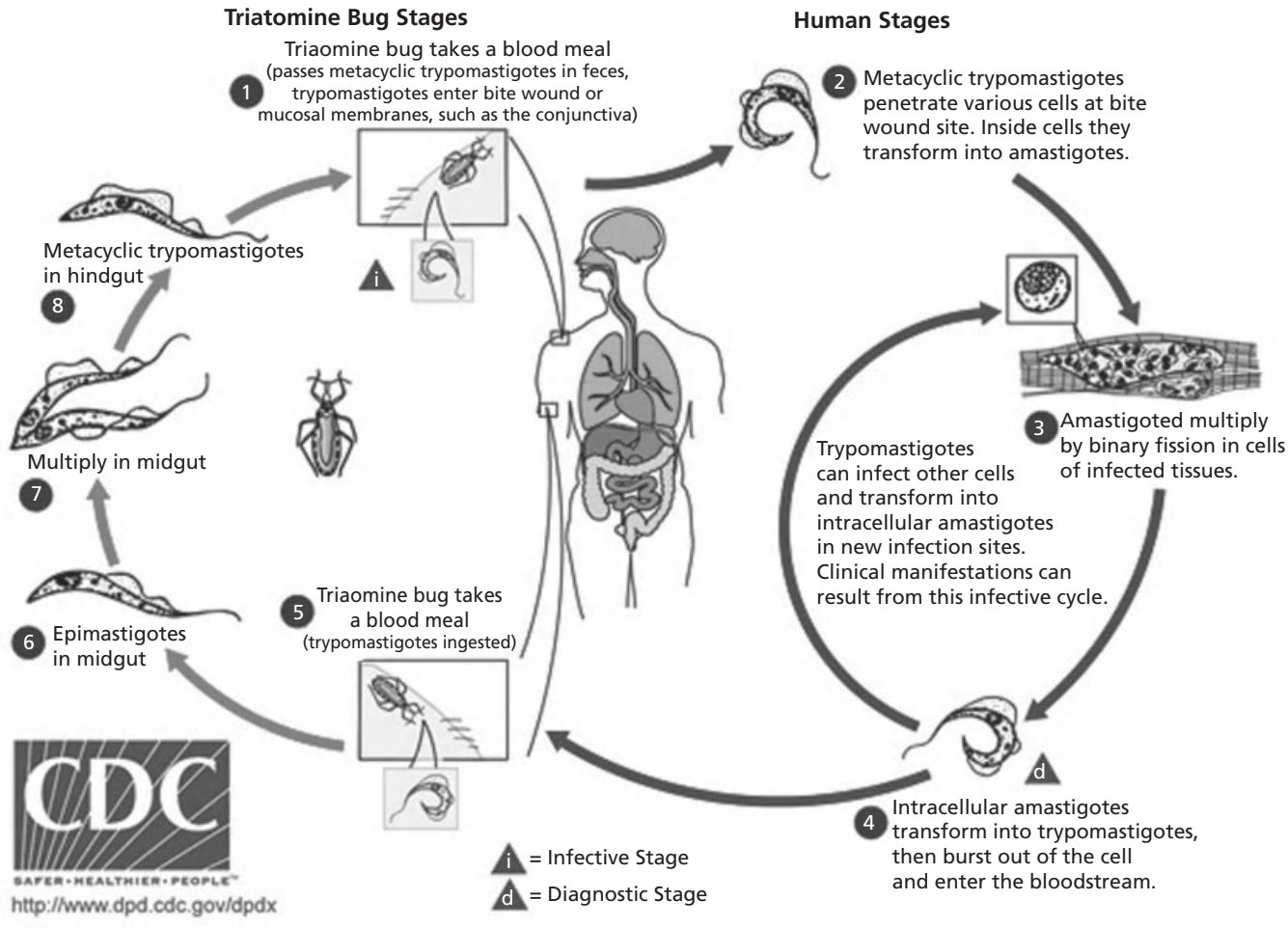

Figure 9.4 Life cycle of *Trypanosoma cruzi*. Used with permission from the Centers for Disease Control and Prevention.

American trypanosomiasis

This infection is only seen in the American continent. The parasite, *Trypanosoma cruzi,* is morphologically different to the African form and causes a completely different disease. It is endemic in rural areas of South and Central America.

Parasite life cycle

T. cruzi is transmitted through the bite of reduviid (triatomine) bugs (*see* Figure 9.4), also known as kissing bugs. These are mainly forest-dwelling insects, but most vector-borne transmission is due to five species that have become adapted to colonise domestic dwellings, living in the thatch and walls of poor-quality housing. They are large and easily recognisable. Biting occurs at night and all stages take a blood meal. The parasite is passed in faeces as the bug feeds. As the bite is scratched by the host, faeces containing the metacyclic trypomastigote stage contaminate the wound and the parasite is introduced to the host. The reservoir is in humans and domestic mammals, along with armadillos and opossums. Oral transmission via food or sugar cane juice contaminated by infected bugs may occur. Vertical transmission and infection via blood transfusion are important routes of infection and can take place in non-endemic areas. Imported cases in travellers are very rare, as exposure to the vector is most commonly seen only after prolonged stays in poor accommodation in rural areas.

Acute infection is rarely symptomatic. Some patients may complain of oedema around the bite site (a chagoma) or around the eye (Romaña's sign), associated with fever and lymphadenopathy. Many patients are asymptomatic at this time and only present after a long latent period with

symptoms of chronic disease. The parasite will infiltrate cardiac conducting tissue, cardiac muscle and smooth muscle of the gastrointestinal tract. Cardiac complications are most common and include various degrees of heart block, arrythmias, cardiomyopathy and cardiac aneurysm. Intestinal disease may result in megaoesophagus or megacolon [24]. Chagasic encephalitis is increasingly recognised to be associated with HIV co-infection [25, 26].

Epidemiology

Reduviid bugs are endemic throughout Central and South America. There are estimated to be 50,000 new cases of Chagas disease annually and a total of 8–9 million infected people throughout the continent [27]. Cases are most commonly seen in rural areas but increasingly in urban areas due to mass urban migration and associated poor-quality living conditions. *T. cruzi* can also be transmitted through intravenous drug use, vertical transmission and blood transfusion [24]. Due to the indolent nature of the infection, cases are often diagnosed decades following exposure to *T. cruzi*. Infection in travellers is extremely rare, but risk factors include rural travel and prolonged stays in poor-quality village accommodation such as huts. In contrast, there is a significant burden of Chagas disease, often in the indeterminate phase, in Latin American migrants.

Diagnosis

Acute phase: microscopy of peripheral blood for trypomastigotes. PCR where available.

Chronic phase: antibody detection by ELISA or IFAT; PCR; haemoculture. Xenodiagnosis by feeding clean, uninfected bugs on the patient is less commonly used since the advent of PCR.

Proven cases should be managed in a specialist centre.

Treatment

Antiparasitic drug therapy with benznidazole or nifurtimox. Bern *et al*. [28] recommend its use for all cases of acute and congenital Chagas disease; reactivated infection; and chronic *T.cruzi* infection in individuals 18 years or younger. Their view is that it should generally be offered to those aged 19 to 50 years without advanced heart disease and that it is optional for those over 50, while treatment should be strongly considered for previously untreated individuals with *T. cruzi* and HIV co-infection and for patients awaiting organ transplantation.

Supportive therapy, including surgery where necessary, is given as required for cardiac complications and megasyndromes.

Control

The mainstay is vector control by indoor residual insecticide spraying and improvement of housing to prevent bugs becoming established in cracked walls and thatched roofing. The bug is not able to live in concrete walls or metal roofing [29]. Sugar cane presses and other food preparation facilities should be protected from possible contamination by infected reduviid bugs. Serological screening of blood donations and early detection and treatment of congenitally infected infants are also important, especially once vectorial transmission has been interrupted in a given region.

Prevention

There are very little data regarding prevention of South American trypanosomiasis in travellers, as the infection is very rarely reported in that group. Travellers who are expecting to spend time in rural forested areas, particularly if living or sleeping in local accommodation should be advised that this will increase their bite risk. It is advisable for travellers to such locations to sleep under a mosquito net and treat bedding with an insecticide to prevent bites. Where possible they should sleep in accommodation where the walls have been sprayed with a residual insecticide.

Filariasis

Filariasis encompasses a wide range of clinical diseases caused by filarial nematodes. They are found exclusively in the tropics and subtropics, predominately in sub-Saharan Africa and Southeast Asia. They are all vector borne, with the parasite being transmitted to humans through the bite of an infected mosquito.

Filariasis can be divided into three common clinical phenotypes: lymphatic filariasis caused by *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*; onchocerciasis caused by *Onchocerca volvulus*; and loiasis caused by *Loa loa* [21]. It is beyond the scope of this chapter to describe these diseases in detail.

Filariasis and travellers

Filarial infections are rare in returning travellers. The Geosentinel network has recorded the highest number of returning travellers with filariasis and the largest groups of cases were in people visiting friends and relatives in endemic countries, missionaries and volunteers. The single case acquired through short-term travel in that series was due to *O. volvulus* [30].

Diagnosis

Lymphatic filariasis: day blood (taken between 12 noon and 2pm) and night blood (taken between midnight and 2am) examination for microfilariae. Serology for antifilarial antibody. A rapid card test for *Wuchereria bancrofti* antigen is available in some countries.

Onchocerciasis: skin snips for microfilariae; serology for antifilarial antibody; histology of excised nodules.

Loiasis: day blood (taken between 12 noon and 2pm) examination for microfilariae. Serology for antifilarial antibody.

If any form of filariasis is suspected clinically, expert medical advice should be sought regarding the appropriate investigations and treatment.

Treatment

Cases of filariasis should be managed by those experienced in the care of helminthic diseases and detailed discussion of treatment for the different filariases is beyond the scope of this chapter. An outline of the treatment used is give below.

Lymphatic filariasis

Diethylcarbamazine citrate (DEC) is used for individual cases. An 8-week course of doxycycline directed against endosymbiont *Wolbachia* in the adult filarial worm has also been used. In filaria-endemic areas the Global Programme to Eliminate Lymphatic Filariasis undertakes single-dose annual mass drug treatment for 4 to 6 years, using either albendazole plus ivermectin or albendazole plus DEC.

Onchocerciasis

Ivermectin kills microfilariae but not adult worms, so ivermectin therapy needs to be repeated at 6- to 12-month intervals until the adult worms have died, which may take as long as 12 years. Doxycycline, given orally for 6 weeks, can be used against adult worms via its action on endosymbiont *Wolbachia*. Nodulectomy is sometimes practised for nodules (containing adult worms) on the head in an attempt to reduce eye infection with microfilariae.

Loiasis

Cases without detectable microfilariae in the peripheral blood are treated with DEC. Steroid cover is given to those in whom microfilariae are seen. If the microfilarial count is very high, albendazole can be used instead of DEC. Where available, apheresis can be used to reduce the microfilarial load prior to drug therapy.

Control

The Onchocerciasis Control Programme (OCP) covered nine West African countries and ran from 1974 to 2002. The programme began with aerial insecticide spraying to kill blackfly larvae. Mass treatment with ivermectin was combined with spraying from 1987 and even used alone in some regions. WHO reports that the OCP prevented 600,000 cases of blindness [31]. The African Programme for Onchocerciasis Control (APOC) began in 1995 and has been extended to 2015. It covers 19 countries and is based on community directed treatment with ivermectin. WHO states that APOC aims to prevent over 40,000 cases of blindness each year [32].

Lymphatic filariasis is also subject to mass treatment programmes. Anti-mosquito measures deployed as part of malaria control can also benefit control of lymphatic filariasis.

Prevention

Any traveller visiting an endemic area for a prolonged period of time, particularly if they are returning to visit friends and relatives or going to work in a rural area, should be advised regarding the risk of filariasis. Measures taken to reduce insect bites (protective clothing, impregnated bed nets, insecticides) will assist with protection against filariasis.

Onchocerciasis is transmitted by blackflies, which breed in fast-flowing water and bite when humans visit the water for washing or drinking. As a result of disease control measures, the incidence of this infection is falling dramatically. Travellers should be advised to seek local advice and avoid travelling on or engaging in activities in fast-flowing water in this region.

Babesiosis

Babesia are protozoan parasites of wild and domestic mammals transmitted by Ixodid ticks. Human babesiosis is a zoonosis and humans represent a dead-end host for the parasite. The disease is rare in travellers.

Infection with bovine babesias

Fewer than 40 cases of human infection with bovine babesias have been formally reported in Europe since the late 1950s. They are usually due to *Babesia divergens*, and previous splenectomy is a major risk factor for acquiring infection. The illness presents as a fulminant infection with prostration, fever, jaundice and haemoglobinuria. It may only be diagnosed post-mortem and may be misdiagnosed as malaria, leptospirosis or viral hepatitis.

Infection with rodent babesias

This is due to *Babesia microti*, whose normal host is the mouse *Peromyscus leucopus*. Most cases are reported from the north-eastern coastal region of the United States. The local tick vector is *Ixodes dammini*. In addition to the mouse, *I. dammini* nymphs feed on deer, but these large animals are not susceptible to *B. microti*.

I.dammini also transmits *Borrelia burgdorferi*, the causal agent of Lyme disease, so co-infection of humans with both organisms is sometimes found in that region. In contrast, these organisms have different vectors in the UK; *Ixodes trianguliceps* for *B. microti* and *Ixodes ricinus* for *B. burgdorferi*. *B. microti* may also be transmitted through blood transfusion. Most human infections are subclinical, but, where present, features of human *B. microti* infection include fever, myalgia and, in severe cases, pronounced haemolytic anaemia and acute renal failure [33]. *B. microti* has been reported as a chronic severe infection in HIV-positive individuals [34].

Epidemiology

B. divergens or *B. bovis* infections of humans are found where splenectomised humans are exposed to tick bite on land grazed by infected cattle.

Most cases of *B.microti* infection have occurred in the north-eastern coastal region of the US, with occasional reports from California, Georgia and Missouri. The animal reservoir is the mouse. While *I. dammini* nymphs also feed on deer, these large animals are not susceptible to *B. microti*.

Reports of travel-associated *Babesia* infection are rare, with a few reported isolated case reports only of disease acquired in the US imported into Canada and Europe [35–37].

Diagnosis

The mainstay of laboratory diagnosis is blood film examination. The parasite may be confused with trophozoites of *Plasmodium falciparum* by inexperienced microscopists, but there are important differences [21]. Serology is useful in some cases of *B. microti* infection but is of little benefit in acute infection. PCR is available in a few centres.

Treatment

Bovine babesias: there are no controlled trials of the treatment of human infection by bovine babesias. Quinine plus clindamycin plus exchange blood transfusion should be used. Atovaquone is active against *B. divergens in vitro*.

Rodent babesias: combination therapy with quinine plus clindamycin or with atovaquone plus azithromycin is effective.

Control

Tick control is notoriously difficult, as the incidence of Lyme disease caused by *Borrelia spp* attests. Control programmes have been attempted using insecticides applied to deer, which have met with limited success [38].

Prevention

Avoiding the bite of the *Ixodes* tick is the mainstay of prevention of babesiosis, and precautions are similar to those needed to prevent Lyme disease [39]. Travellers who have been splenectomised or who are HIV positive should be warned particularly about the potential severity of babesiosis.

When walking or exercising in endemic areas, legs and feet should be covered in thick clothes, ideally impregnated with permethrin. Insect repellent should also be used. If camping, tents should also be impregnated with insecticide. These precautions should be applied particularly to those undertaking adventure travel in the north-eastern US. After potential exposure the body should be checked for the presence of ticks. If found they should be removed, with a technique to ensure the tick's mouthparts are also removed. No antimicrobial prophylaxis after tick bite is indicated for prevention of babesiosis, but this infection should be included in the differential diagnosis in any patient who experiences fever or haematuria following exposure to ticks in babesia-endemic regions.

Schistosomiasis

Schistosomiasis (also known as bilharziasis) is one of the commonest parasitic diseases worldwide and is endemic in 76 countries [40]. Schistosomes are a complex group of fluke parasites, which have a subtropical and tropical distribution. The parasite has a complicated life cycle but is not classically vector borne. The 'vector' is the fresh water snail that is essential for the life cycle but is an intermediate host rather than a direct human vector. The disease is divided clinically into two main manifestations, affecting either the genitourinary system (*S. haematobium*) or the gastrointestinal system (*S. mansoni* and *S. japonicum*).

Parasite life cycle

The life cycle of schistosomiasis is complicated but essentially the same for all different species. The main reservoir and host is humans, and the intermediate host is a fresh water snail of the following genera: *Bulinus (S. haematobium), Biomphalaria (S. mansoni) and Oncomelania (S.*

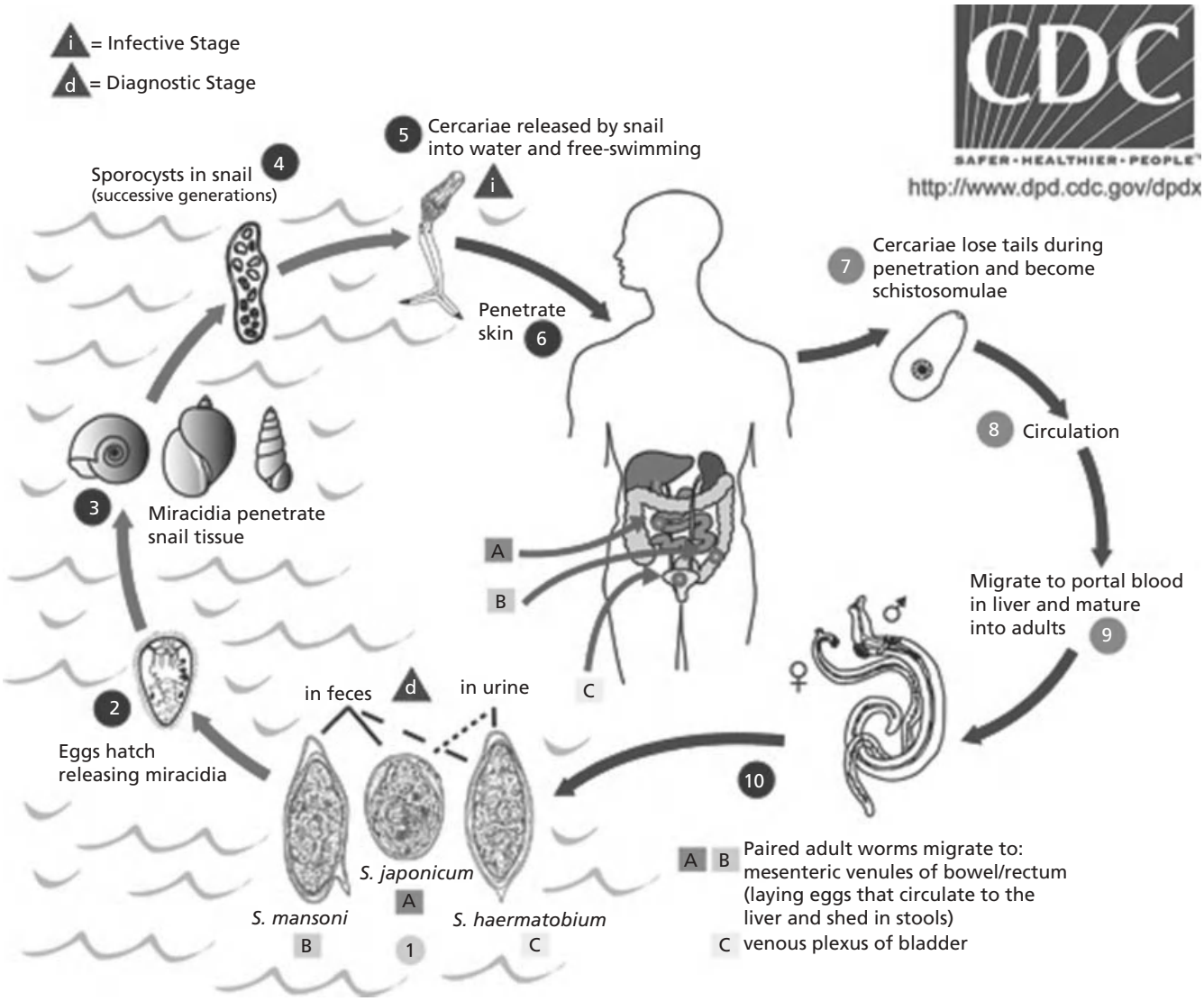

Figure 9.5 Life cycle of the Schistosomes. Used with permission of the Centers for Disease Control and Prevention.

japonicum). As ova are passed in urine or faeces from humans into the water, miracidia hatch. These then penetrate the body of the snail, and the parasite matures. Cercariae are released from the snail into the water and penetrate human skin when immersed in water (*see* Figure 9.5). The snail is found in reedy areas at the edge of the lake, but the cercariae may be found throughout sampled lakes. Water conditions are important for the snail to thrive, requiring temperatures between 10 and 30°C. Therefore schistosomiasis is not only found in tropical zones, most commonly the great lakes of Africa, but also in the Middle East, parts of South America, China and South East Asia. Detailed information on geographical distribution is available from WHO at http://www.who.int/wormcontrol/documents/maps/country/en/.

Epidemiology

Schistosomiasis is a huge problem and is found wherever people are living on or near fresh water borders throughout Africa and in other areas in the tropics. An estimated 187 million cases occur worldwide, most of them in sub-Saharan Africa [40]. Transmission is associated with conditions of poverty and poor sanitation. Within each country the epidemiology varies according to different fresh water management systems, including sanitation and irrigation.

Epidemiology of schistosomiasis in travellers

Schistosomiasis is seen regularly in travellers, particularly following travel to sub-Saharan Africa. *S. haematobium* and *S. mansoni* are found throughout the great African lakes and rivers, most recognised (due to the large number of travellers visiting and acquiring infection) are the Nile and Lakes Malawi and Victoria. These infections are common throughout Africa, and are also found in the islands of the Indian Ocean (with the exception of Mauritius, where schistosomaisis has been eradicated). *S. haematobium* is also found in the Middle East and very rarely in Maharashtra state in India. *S. japonicum* is exclusively found in China and parts of Indonesia and the Philippines. Infection here is commonly associated with paddy fields and rice cultivation and therefore travellers are at much lower risk than are the local population.

In a large survey of purely travel-associated schistosomiasis from the Geosentinel network, 407 cases were identified between 1997 and 2008, 83% of which were acquired in Africa [41].

Swimming is the most common method of transmission in travellers, but it is also possible to be infected through showering or bathing in lake water, and this is recognised particularly in those staying in hotels on the edge of popular tourist destination lakes. The most common source of exposure is traditionally lakes, due to the large numbers of tourists who swim and undertake water sports in them. However, wading or paddling in shallow water is also associated with a transmission risk.

Clinical features

Infection may be asymptomatic in lightly infected individuals. Where symptoms occur they are stage-dependent. Cercarial penetration of the skin may produce swimmers' itch, or cercarial dermatitis, an itchy papular rash that subsides in a few days. From 4 weeks onwards there may an acute febrile illness, often complicated by wheeze, urticaria and eosinophillia, called Katayama fever. This is associated with the onset of egg laying by the female worm. It is not invariably found but is most common in *S. japonicum* and *S. mansoni* infection, though it can also occur with *S. haematobium*. Chronic disease is caused by the host's reaction to eggs produced by adult parasites residing in the venous system of the intestine or bladder. These eggs are shed via either the gut (*S. mansoni* and *S. japonicum*) or the bladder (*S. haematobium*). Reaction to the eggs causes chronic inflammation, fibrosis and scarring, and is associated with development of carcinoma of the bladder, most commonly of the squamous type, in long-standing urinary schistosomiasis, and with portal fibrosis, leading to portal hypertension, in *S. mansoni* and *S. japonicum* infection. In adult females, chronic urinary schistosomiasis is associated with an increased risk of having HIV infection [42].

Diagnosis

As both early and chronic infection may be asymptomatic, the mainstay of diagnosis in returning travellers is through serology, which is highly sensitive. Ova may be demonstrated in urine or faecal samples, or from biopsies of bladder or rectal mucosa in the event of haematuria or rectal blood loss. Travellers who are potentially going to be exposed to schistosomiasis through travel should be advised to attend screening with serology 3 months or more after exposure, particularly if one of the group has been symptomatic or diagnosed on the basis of positive serology [41].

Treatment

All species of schistosomes are sensitive to praziquantel, a well-tolerated anthelminthic. Treatment should always follow advice from or clinical review at a specialist centre. Katayama fever is treated with praziquantel under corticosteroid cover. As praziquantel is only active against the mature adult stages of the parasite and immature flukes may still be present when Katayama fever presents, praziquantel treatment should be repeated after another 3 months.

Control

Schistosomaisis control has focused on snail control, improving sanitation, water treatment with cercaricides and mass treatment with praziquantel. There have been some notable successes, for example eradication in Mauritius [43], and the Carter Center and the Schistosomiasis Control Initiative have both undertaken substantial work on control. It is hoped that with further investment through philanthropic and public funding the burden of this infection will be reduced long term.

Prevention

Avoiding fresh water exposure is the mainstay of prevention of schistosomiasis. Travellers should be warned about the risk of swimming in tropical lake water, particularly in sub-Saharan Africa and also of the risk of bathing or showering in lake water. Cercariae are killed by chlorination and heating water to 50°C. Fine water filters are not reliable to remove cercariae. Ideally, hotel accommodation in endemic areas should have chlorinated water in showers and baths. If the traveller does swim in potentially infected water there is

some evidence that post-exposure application of DEET to the skin may prevent schistosomiasis in those with limited exposure [44]. The authors suggest it could be applied 8 to 12 hours after exposure.

Conclusions

Among the vector-borne parasitic diseases malaria must always be excluded and treated as a priority. Other imported vector-borne parasitic diseases such as leishmaniasis and trypanosomiasis are associated with exposure to specific vectors with well-defined epidemiological risks of infection, as are rarer infections including filariasis and babesiosis. As yet there are no vaccines licensed for human use to prevent infection with the parasites mentioned in this chapter. The mainstays of their prevention are vector and bite avoidance. Awareness of the vectors and their habitats is therefore essential for all travel medicine practitioners. There is no suitable drug prophylaxis for any of these parasitic infections.

Schistosomiasis is more common in travellers than the vector-borne infections discussed in this chapter and detailed knowledge of its epidemiology and prevention is extremely important for travel medicine. Advice to avoid swimming, paddling or washing in fresh water lakes and rivers, particularly in sub-Saharan Africa, should be given to all people intending to travel to this region, as well as advice to attend screening on return should potential exposure have occurred.

HIV-positive travellers should be given especially detailed advice to avoid all vector-borne and associated parasitic infections.

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References

1. Freedman DO *et al.* (2006) Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med* **354**(2): 119–130.
2. Desjeux P (2004) Leishmaniasis. *Nat Rev Microbiol* **2**(9): 692.
3. Cruz I *et al.* (2002) Leishmania in discarded syringes from intravenous drug users. *Lancet* **359**(9312): 1124–1125.
4. Morgan DJ *et al.* (2007) Cutaneous leishmaniasis during pregnancy: exuberant lesions and potential fetal complications. *Clin Infect Dis* **45**(4): 478–482.
5. Killick-Kendrick R (1990) Phlebotomine vectors of the leishmaniases: a review. *Med Vet Entomol* **4**(1): 1–24.
6. Costa CH (2008) Characterization and speculations on the urbanization of visceral leishmaniasis in Brazil. *Cad Saude Publica* **24**(12): 2959–2963.
7. Salomon OD *et al.* (2008) Urban distribution of Phlebotominae in a cutaneous leishmaniasis focus, Argentina. *Mem Inst Oswaldo Cruz* **103**(3): 282–287.
8. Reithinger R *et al.* (2007) Cutaneous leishmaniasis. *Lancet Infect Dis* **7**(9): 581–596.
9. Halsey ES *et al.* (2004) Visceral leishmaniasis in a soldier returning from Operation Enduring Freedom. *Mil Med* **169**(9): 699–701.
10. Scarisbrick JJ *et al.* (2006) Clinical features and diagnosis of 42 travellers with cutaneous leishmaniasis. *Travel Med Infect Dis* **4**(1): 14–21.
11. Weina PJ *et al.* (2004) Old world leishmaniasis: an emerging infection among deployed US military and civilian workers. *Clin Infect Dis* **39**(11): 1674–1680.
12. Zeegelaar JE *et al.* (2005) Changing pattern of imported cutaneous leishmaniasis in the Netherlands. *Clin Exp Dermatol* **30**(1): 1–5.
13. Lawn SD *et al.* (2004) New world mucosal and cutaneous leishmaniasis: an emerging health problem among British travellers. *QJM* **97**(12): 781–788.
14. Faber WR *et al.* (2003) Value of diagnostic techniques for cutaneous leishmaniasis. *J Am Acad Dermatol* **49**(1): 70–74.
15. Gonzalez U *et al.* (2008) Interventions for Old World cutaneous leishmaniasis. *Cochrane Database Syst Rev* (4): CD005067.
16. Amora SS *et al.* (2009) Control of phlebotomine (Diptera: Psychodidae) leishmaniasis vectors. *Neotrop Entomol* **38**(3): 303–310.
17. Fevre EM *et al.* (2008) The burden of human african trypanosomiasis. *PLoS Negl Trop Dis* **2**(12): e333.
18. World Health Organization (2012) Human African trypanosomiasis. http://www.who.int/trypanosomiasis_african/en/ (accessed 8 May 2012).
19. Gautret P *et al.* (2009) Imported human African trypanosomiasis in Europe, 2005–2009. *Euro Surveill* **14**(36): pii: 19327.
20. Jelinek T *et al.* (2002) Cluster of African trypanosomiasis in travelers to Tanzanian national parks. *Emerg Infect Dis* **8**(6): 634–635.
21. Cook GC and Zumla A (eds) (2009) *Manson's Tropical Diseases*, 22nd edn. Saunders Elsevier, London.
22. Brun R *et al.* (2010) Human African trypanosomiasis. *Lancet* **375**: 148–159.
23. Welburn SC *et al.* (2006) Crisis, what crisis? Control of Rhodesian sleeping sickness. *Trends Parasitol* **22**(3): 123–128.
24. Moncayo A and Ortiz Yanine MI (2006) An update on Chagas disease (human American trypanosomiasis). *Ann Trop Med Parasitol* **100**(8): 663–677.
25. Cordova E *et al.* (2008) Reactivation of Chagas disease with central nervous system involvement in HIV-infected patients in Argentina, 1992–2007. *Int J Infect Dis* **12**(6): 587–592.
26. Diazgranados CA *et al.* (2009) Chagasic encephalitis in HIV patients: common presentation of an evolving epidemiological and clinical association. *Lancet Infect Dis* **9**(5): 324–330.
27. Hotez PJ *et al.* (2008) The neglected tropical diseases of latin america and the Caribbean: a review of disease burden and distribution and a roadmap for control and elimination. *PLoS Negl Trop Dis* **2**(9): e300.

28. Bern C *et al.* (2007) Evaluation and treatment of Chagas disease in the United States – a systematic review. *JAMA: J Am Med Assoc* **298**(18): 2171–2181.
29. Moncayo A and Silveira AC (2009) Current epidemiological trends for Chagas disease in Latin America and future challenges in epidemiology, surveillance and health policy. *Mem Inst Oswaldo Cruz* **104** Suppl. 1): 17–30.
30. Lipner EM *et al.* (2007) Filariasis in travelers presenting to the GeoSentinel Surveillance Network. *PLoS Negl Trop Dis* **1**(3): e88.
31. World Health Organization (2012) Onchocerciasis Control Programme (OCP). www.who.int/blindness/partnerships/onchocerciasis_OCP/en/ (accessed 6 May 2012).
32. World Health Organization (2012) African Programme for Onchocerciasis Control (APOC). www.who.int/blindness/partnerships/APOC/en/ (accessed 6 May 2012).
33. Vannier E *et al.* (2008) Human babesiosis. *Infect Dis Clin North Am* **22**(3): 469–488, viii–ix.
34. Krause PJ *et al.* (2008) Persistent and relapsing babesiosis in immunocompromised patients. *Clin Infect Dis* **46**(3): 370–376.
35. Nohynkova E *et al.* (2003) A case of Babesia microti imported into the Czech Republic from the USA. *Cas Lek Cesk* **142**(6): 377–381.
36. Loutan L *et al.* (1993) Imported babesiosis diagnosed as malaria. *Lancet* **342**(8873): 749.
37. Humiczewska M and Kuzna-Grygiel W (1997) A case of imported human babesiosis in Poland. *Wiad Parazytol* **43**(2): 227–229.
38. Brei B *et al.* (2009) Evaluation of the United States Department of Agriculture Northeast Area-wide Tick Control Project by meta-analysis. *Vector Borne Zoonotic Dis* **9**(4): 423–430.
39. Clark RP and Hu LT (2008) Prevention of Lyme disease and other tick-borne infections. *Infect Dis Clin North Am* **22**(3): 381–396, vii.
40. The World Bank Group (2006) Disease Control Priorities Project. http://dcp2.org/pubs/DCP/24/ (accessed 6 May 2012).
41. Nicolls DJ *et al.* (2008) Characteristics of schistosomiasis in travelers reported to the GeoSentinel Surveillance Network 1997–2008. *Am J Trop Med Hyg* **79**(5): 729–734.
42. Stoever K *et al.* (2009) HIV/AIDS, schistosomiasis, and girls. *Lancet* **373**(9680): 2025–2026.
43. Dhunputh J (1994) Progress in the control of schistosomiasis in Mauritius. *Trans Roy Soc Trop Med Hyg* **88**(5): 507–509.
44. Jackson F *et al.* (2003) Schistosomiasis prophylaxis in vivo using N,N-diethyl-m-toluamide (DEET). *Trans Roy Soc Trop Med Hyg* **97**(4): 449–450.

Chapter 10 Malaria and travellers

MALARIA

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Malaria is one of the leading causes of death and morbidity worldwide with 3 billion people at risk from infection in 106 countries endemic for malaria. In 2010, there were an estimated 216 million episodes of malaria and an estimated 655,000 deaths, mostly in African children under 5 years old [1]. There are more than 120 species in the Plasmodium genus, but it is *P. falciparum, P. vivax, P. ovale* and *P. malariae* that cause human disease. Until recently, the other species were thought only to infect animals. However, *P. knowlesi*, a parasite that usually infects monkeys in Southeast Asia, has now been described as causing illness in Malaysia and may be considered the fifth plasmodium species to cause human disease [2]. The geographical distributions of the species vary; *P. vivax* infection has the widest geographical range, but predominates in the Indian subcontinent, Mexico, Central America and China. Vivax accounts for more than half of all malaria infections outside Africa and approximately 10% of those in Africa [3]. *P. ovale* is found mainly in West Africa and *P. malariae* has a patchy distribution throughout tropical and temperate regions. *P. falciparum,* found throughout the tropics, is responsible for the vast majority of deaths and morbidity. In Africa, falciparum is the cause of more than 75% of malaria infections.

Malaria parasites are transmitted to humans at the time of biting by the female *Anopheles* mosquito. Malaria sporozoites are inoculated in the saliva of the mosquito. These invade hepatocytes in the liver and undergo a variable period of replication, the 'exo-erythrocytic' cycle. The duration of this stage depends on the species involved, the presence of antimalarial drugs in the blood, and other host and parasite factors. For *P. falciparum*, this period is around 10 days. At the end of this period, millions of merozoites are released from the liver to invade circulating red blood cells. Several rounds of asexual replication then take place within the infected red cells in the blood, the 'erythrocytic' cycle. During this time, the parasite develops from the ring stage morphology to the trophozoite stage. After approximately 48 or 72 hours, depending on the infecting species, infected red cells packed with mature trophozoites (schizonts) rupture, releasing more merozoites (to infect more red cells) and other parasite antigens. At this point, clinical symptoms first occur.

Subsequently, some of the merozoites differentiate into male or female gametocytes, the stage of the parasites that is infectious to biting mosquito; gametocytes are not pathogenic. Falciparum gametocytes appear in the peripheral blood around 10 days after the peak in numbers of asexual ring forms. In other malaria species, gametocytes appear earlier, around the same time as the peak in asexual forms [4]. Gametocytes are taken up by the mosquito during a blood meal and around 10 days later sporozoites appear in mosquito saliva, ready to cause further human infection. Ovale and vivax have an additional life stage with the development of a dormant liver infection in humans, called a 'hypnozoite', which can cause relapse of malaria symptoms and parasitaemia many years after successful treatment of the primary infection. The lifecycle of the malaria parasites in humans and mosquitoes is shown in Figure 10.1.

Falciparum malaria is much more pathogenic than the other malaria species because it has the highest replication rate and uniquely, it causes infected erythrocytes in the

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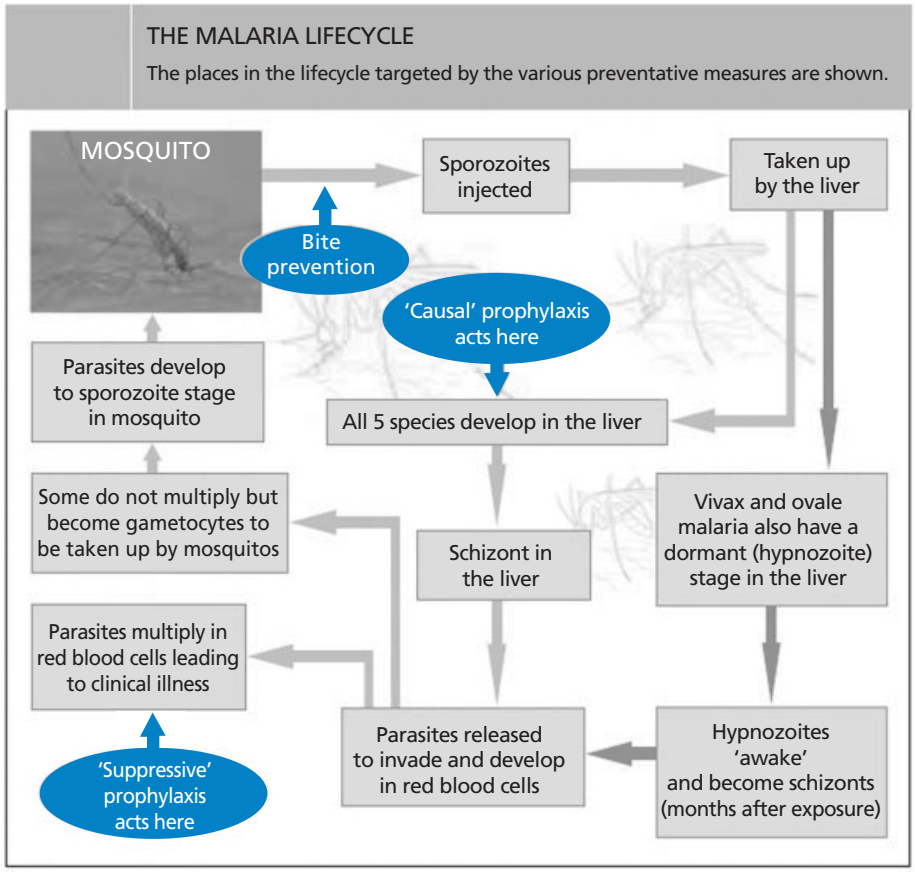

Figure 10.1 The lifecycle of malaria parasites in humans and mosquitoes. (From the Chiodini PL *et al.* [31])

peripheral blood to adhere to each other and to the endothelial walls of small vessels. This process results in the sequestration of large numbers of parasitised red cells in microvascular beds in the brain, gut, spleen and other organs, and leads to the severe pathology seen with falciparum [5].

Malaria clinical features and immunity

The consequences of infection with *P. falciparum* malaria can broadly be classified into three syndromes: asymptomatic infection, uncomplicated malaria and severe malaria. Asymptomatic infection occurs when an individual is able to tolerate the presence of parasitaemia without exhibiting symptoms, and is seen in older children and adults who grow up in areas of high malaria transmission. Asymptomatic infection is not always clinically insignificant and may lead to anaemia, and infected individuals are infectious to mosquitoes and a significant reservoir of infection [6]. This immune tolerance in known as premunition and is due to the development of malaria-specific partial immunity as a result of repeated falciparum infections (usually with a limited number of locally prevalent isolates). In high transmission areas, for example much of sub-Saharan Africa, this immunity is built up during early childhood [7] and comes at a great cost, with malarial morbidity and mortality concentrated in young children [8]. In contrast, travellers and people living in countries with low-intensity or sporadic malaria transmission develop little immunity, and malaria infection causes symptomatic disease in all age groups.

The clinical features of uncomplicated or non-severe malaria are non-specific and include fever, malaise, headache, myalgia, anaemia and minor gastrointestinal symptoms. Approximately 1–2% of uncomplicated infections progress to severe and life-threatening malaria characterised by the development of organ or tissue complications. Severe malaria has a mortality rate of between 15 and 50% depending on the setting [9]. Prompt effective treatment when symptoms occur reduces the risk of progression to severe

Table 10.1 Clinical features of severe malaria in non-immune adults [10]

Impaired consciousness or seizures
Hypoglycaemia (<2.2 mmol/l)
Haemoglobin <8 g/dl
Spontaneous bleeding or disseminated intravascular coagulation
Haemoglobinuria
Renal impairment
Acidosis (pH < 7.3)
Pulmonary oedema/Acute respiratory distress syndrome
Shock

disease. Clinical features suggestive of adult severe disease are shown in Table 10.1 [10].

Malaria during pregnancy is a risk factor for the development of severe disease in both non-immune and semi-immune (especially primigravidae) women and a major risk factor for fetal growth retardation and infantile death [11]. HIV (human immunodeficiency virus)-infected individuals appear to be at greater risk of failing treatment and of developing severe disease [12], and several host genetic factors influence the risk that *P. falciparum* infection will lead to severe disease. The best documented of these are the protection afforded by the heterozygous state for haemoglobin S (the sickle cell trait) [13] and by the alpha+ thalassemias [14].

The features of severe malaria in children growing up in high malaria transmission areas are predominantly severe anaemia, altered consciousness and convulsions, acidosis/respiratory distress and hypoglycaemia [15]. One or several of these may be present in an individual, the prognosis worsening with the number of complications. Intravascular haemolysis with haemoglobinuria, renal failure, acute respiratory distress syndrome and disseminated intravascular coagulation are rare in children.

Malaria drug resistance patterns worldwide

Drug resistant *P. falciparum* is now widespread throughout the world with resistance to most of the drugs available to treat malaria and to several drugs previously used as prophylaxis. Resistance to chloroquine (CQ), sulfadoxine-pyrimethamine (SP) and mefloquine was first observed in parasites from the Thai borders with Burma and Cambodia, before spreading to other parts of Asia and on to Africa [16]. With the exception of parts of South America and some countries in the Middle East and Asia, CQ and/or proguanil (an anti-folate drug like SP) cannot now be recommended for malaria prophylaxis or treatment due to resistance. The efficacy of SP for treatment (and by implication prophylaxis) is also poor in most regions of the world. Ongoing surveillance to monitor resistance patterns within countries is important to guide future treatment and prophylaxis options.

The consequences of drug resistance include more cases of severe disease and death, and economic costs as a result of time off work and the need to treat resistant parasites with more expensive agents. The development and spread of chloroquine resistance is thought to have led to a two- to 11-fold rise in the malaria-associated mortality in African children [17]. Of great concern, there have been recent reports of a decline in *P. falciparum* sensitivity to artemisinins in the Thai-Cambodian border region [18]. Artemisinins are derived from the Chinese medicinal herb sweet wormwood or 'qing hao' and have been used to treat fever since the 4th century AD. They were 'rediscovered' around 1971 by researchers in China and found to be the most potent of all the antimalarial drugs [19]. They are active against all parasite stages, causing rapid clearance of parasites and preventing young ring stages from sequestering. They also reduce gametocytes, the parasite stage responsible for onward transmission. This efficacy means that they have become the mainstay of therapy throughout the world, although they are not used for prophylaxis. Quinine remains efficacious in clinical trials against multidrug-resistant *P. falciparum* in most parts of the world, though in parts of Southeast Asia there is evidence of a decline in the efficacy of the drug indicated by longer parasite and fever clearance times [20].

Chloroquine-resistant vivax is reported in Papua New Guinea and Indonesia [21], but its spread seems relatively limited. Resistant strains of ovale, malariae and knowlesi malaria have not been reported. Primaquine is the only drug currently licensed for the radical cure of vivax and ovale (for the elimination of hypnozoites). Reduced susceptibility to primaquine has been reported in the Chesson strain of vivax in Southeast Asia and higher doses are required to treat this parasite [22].

Malaria infection in travellers

Most cases (90%) of falciparum malaria present within a month of returning from travel, though this can be delayed if antimalarial prophylaxis is taken. More than 95% of cases present within 6 months of exposure [23]. Presentation of non-falciparum malarias may occur much later, with cases sometimes presenting more than a year after travel. Data on the numbers of imported malaria cases are available for several countries. In Europe, France, the UK, Germany and

Italy reports most cases, with the majority due to *P. falciparum*. In Australia, there were 505 reported cases of imported malaria from 2007 to 2008, with 48% of these due to vivax, and 46% to falciparum, reflecting the fact that the Asia-Pacific region was the main destination for Australia travellers [24]. Between 350 and 1,000 malaria cases occur each year in Canada [25, 26]. In the UK in 2010, 1,761 malaria cases were reported, with 72% due to falciparum, 20% due to vivax and there were seven deaths, all due to falciparum. In the US, 1,691 malaria cases were reported in 2010, 58% due to falciparum and 19% vivax [27]. For both the UK and US, the largest at-risk group were residents who travelled to visit friends or relatives overseas (VFR travellers), most commonly in West Africa, and in most cases adequate prophylaxis was not taken. In 2007, only 9% of UK residents and 37% of US residents who caught malaria while visiting friends or relatives overseas took recommended malaria prophylaxis regimens.

Prevention of malaria in travellers

International travel is predicted to grow from 922 million to 1.6 billion international arrivals by 2020 [28], and unless malaria control programmes worldwide impact on malaria transmission, there is likely to be a rise in the numbers of travellers exposed to malaria. The 'ABCD' approach to malaria prevention is shown in Table 10.2.

The risk for a traveller of contracting malaria depends on whether prophylaxis is taken, the countries visited and the season of year; mosquito numbers and transmission rates are higher during the wet season than the dry season. The activities undertaken while in endemic areas will also affect risk; travellers on safari or camping trips will be at higher risk than those in urban areas staying in air-conditioned hotels. Country-specific risk of acquiring malaria have been estimated as around 1 in 150 travellers to Ghana, 1 in 460 to Kenya and 1 in 35,000 to Thailand [29].

Another important consideration for some groups of travellers is the perception of risk. In both the UK and US, 'VFR' travellers are responsible for most imported malaria cases. There is some evidence to suggest that these individuals do not consider malaria a serious risk and are less likely to seek advice prior to travelling [30]. Clearly targeted interventions to increase awareness in this group may have a big impact on the numbers of imported cases.

Table 10.2 The 'ABCD' approach to malaria prevention

A – Assessment and awareness of risk
B – Bite avoidance
C – Chemoprophylaxis
D – Diagnosis and treatment

Mosquito bite avoidance

The female *Anopheles* mosquito, the vector for malaria, bites mainly at night between dusk and dawn, with a peak biting time in Africa at around 2am. Other mosquito-borne diseases, including dengue, yellow fever and some forms of filariasis, are transmitted by day-biting mosquitoes and so in some parts of the world bite avoidance measures are needed both day and night. These methods include repellents applied to skin and clothing, insecticides applied to bednets, clothing and used indoors, clothing to cover exposed skin, and room protection methods including window and door screens and air conditioning [31, 32].

The most effective and well-known repellent against mosquitoes and other biting insects is DEET (diethyl-meta-toluamide) [33]. DEET is applied to exposed skin and is safe in children over 2 months, in breast-feeding mothers and in women in the second and third trimesters of pregnancy [34]. It is available in concentrations ranging from 20 to 50%. Higher concentrations are associated with a longer period of protection; up to 12 h for the 50% formulation. In Canada, the maximum concentration available is 30%. Concentrations higher than 50% are not recommended and provide no additional benefit. Because of the risks of malaria in pregnancy, the UK guidelines recommend 50% DEET for pregnant women. Alternatives to DEET include Icaridin (picaridin), citronella, lemon eucalyptus oil and 3-ethlyaminopropionate (IR3535). Twenty per cent icaridin and 30% lemon eucalyptus oil have been reported to be as effective as lower concentrations of DEET against mosquitoes in some studies, although the duration of protection appears to be shorter than 50% DEET [32]. Citronella provides only a short period of protection, less than 2 h, and requires very frequent reapplication.

Insecticide-treated bednets (ITNs) have been distributed widely in Africa and have been effective in reducing the burden of disease for the people living in malaria-endemic countries [35], and they are also likely to be equally protective in travellers. Nets should be re-treated with pyrethroid insectides, usually permethrin, on a regular basis (usually every 6 months) to maintain their maximal protection. Permethrin can also be applied to clothing and acts both as a repellent and an insecticide, killing mosquitoes on contact. Insecticide sprays and electric 'vapourisers' that heat a tablet of insecticide are safe to use indoors, while mosquito coils are not recommended for indoor use due to the potential hazardous fumes emitted. All are effective at killing mosquitoes and reducing biting. Several alternative mosquito protection methods have not been shown to be effective in trials

and cannot be recommended. These include 'natural' repellents such as garlic, Marmite, vitamin B compounds, bath oils and homeopathic remedies.

Worldwide prophylaxis guidelines

Guidelines are available from a number of countries including the UK, the US and Canada [25, 31, 36]. The choice of regimen is guided by the countries to be visited and the age and other medical conditions of the traveller. In general, the recommendations from these authorities are similar in terms choice of regimen for particular areas and in special patient groups. All include atovaquone-proguanil, mefloquine, doxycycline and chloroquine (or hydroxychloroquine) to be used according to the countries being visited. Proguanil plus chloroquine is recommended in the UK guidelines for some areas with low levels of chloroquine resistance (e.g. parts of India), but this regimen is not recommended by the US or Canadian authorities. In addition, primaquine is recommended in the US and Canada, but not in the UK, as a primary prophylaxis for travellers on short trips to areas with mainly *P. vivax* transmission or those unable to tolerate alternative regimens. More details on these drugs, their contraindications and the use of malaria prophylaxis in special groups are given below.

Treatment of malaria in malaria-endemic countries

To achieve rapid clearance of parasites and slow the rate of development of resistance, the World Health Organization (WHO) recommends artemisinin combination therapies (ACTs) to treat uncomplicated falciparum malaria, using combination treatment principles common to tuberculosis and HIV [37]. Several ACTs are now available, including artemether-lumefantrine and artesunate-amodiaquine, formulated as fixed-ratio tablets, important for patient compliance. ACTs are considerably more expensive than older drugs such as chloroquine and sulfadoxine-pyrimethamine, but their use, and the roll out of ITNs, has been supported financially by international funding initiatives and by pharmaceutical companies providing drugs at cost price. Although there have been problems in the implementation of these policies in some countries due to supply and distribution difficulties, by June 2008, ACTs were first-line treatment choice in 77 *P. falciparum*-endemic countries worldwide [1].

Evidence is now emerging to suggest that in Africa, the widespread use of ACTs and ITNs is resulting in a reduction in malaria transmission in some areas [1, 38]. Optimism, not present for years in malaria control circles, has returned and some have even dared mention the 'eradication' word again [39]. However, multiple difficulties remain, including keeping up with the huge demand for these drugs, widespread use of fake drugs, poor treatment practices and, most worrying of all, the recent reports of a decline in *P. falciparum* sensitivity to artemisinins in the Thai-Cambodian border region [18]. The establishment and spread of artemisinin-resistant parasites from this area would be a public health disaster. Worldwide, artemisinin-containing treatments are an essential component of malaria control programmes today. There are no other treatment options currently available that are as effective as the artemisinins.

Treatment of imported malaria in travellers

Treatment guidelines for imported malaria are available for several countries, including the UK, US, Canada and Australia [10, 25, 40, 41]. In the UK, US and Canada, it is recommended that all patients with falciparum malaria should be admitted to hospital for treatment, although outpatient treatment has been advocated in some European countries and by some UK centres [42, 43]. Approximately 1% of all individuals with imported falciparum malaria die [44], and predicting which patients are most likely to get severe disease or die is difficult. Patients may initially present with low parasitaemias or none of the features usually associated with severe disease (Box 10.1), and then rapidly deteriorate. Young children, the elderly and pregnant women are at particularly high risk of severe disease and require close observation in hospital [15, 45]. It is dangerous to make the assumption that patients brought up in malaria-endemic areas will be immune and not suffer severe disease. Malaria immunity wanes if people are not re-exposed to malaria parasites on a regular basis, so those individuals who have moved away from malaria-endemic areas are also at risk of severe disease [46]. In one prospective study of patients presenting with falciparum malaria to a hospital in London, 4.3% of patients born and brought up in sub-Saharan Africa required intensive-therapy unit (ITU) care during their admission [47].

Treatment options for imported *P. falciparum* infection in travellers are shown in Table 10.1 and are guided by the country in which the infection was acquired and according to whether the individual has severe or uncomplicated disease [10]. Artemether-lumefantrine and atovaquone-proguanil are both licensed in Europe and the US and have advantages over oral quinine due to their shorter treatment duration (3 versus 7 days) and better tolerability. Registration of another ACT, dihydro-artemisinin-piperaquine, is anticipated in Europe in the near future. Mefloquine is

Table 10.3 Treatment options for falciparum malaria in returned travellers

Uncomplicated falciparum malaria	Artemether-lumefantrine (Riamet/CoArtem) orally for 3 days Atovaquone-proguanil (Malarone) orally for 3 days Quinine (or quinidine in US) plus doxycycline, tetracycline or clindamycin orally for 7 days Mefloquine orally, 2 doses separated by 6–12 h Chloroquine* orally for 3 days
Severe falciparum malaria	IV quinine (or quinidine in USA) for 7 days plus doxycycline, tetracycline or clindamycin for 7 days. Step down to oral therapy once tolerated. IV artesunate

*Chloroquine is not recommended treatment for falciparum malaria in the UK or Australia

effective for uncomplicated malaria but poorly tolerated at treatment doses and is not recommended in the UK (but is in the US and Australia) [48]. Chloroquine-sensitive falciparum malaria is limited geographically to parts of Central America and the Middle East. In the US and Canada, chloroquine (or hydroxychloroquine) is recommended to treat falciparum infections acquired in these areas (Table 10.3). In the UK and Australia, however, chloroquine is not recommended to treat falciparum malaria; a decision made on the basis that there are several alternatives and that the risk of treating a potentially chloroquine-resistant infection is too high and clinicians may be unaware of the geographical distribution of chloroquine sensitive and resistant parasites.

For those with features of severe disease, high parasite counts (e.g. ≥2%), pregnant women or those unable to retain tablets, parenteral therapy is required. Intravenous (IV) artesunate has shown a survival advantage in patients (predominantly adults) with severe disease compared with IV quinine in a trial in Asia [49] and now also in children in Africa [50]. The beneficial effect seen in Asia was most marked in those with initial parasitaemias > 10%. Despite this clinical advantage, current UK treatment guidelines still favour IV quinine: the Chinese manufacturer of IV artesunate has not achieved good manufacturing practice (GMP) certification so the product is not licensed. IV artesunate obtained from China is available in some specialist tropical disease centres in the UK for patients with very high parasite counts, very severe disease, deterioration on optimal doses of quinine, cardiovascular disease that increases the risks from quinine or patients with falciparum malaria from Southeast Asia where relative quinine resistance is most likely. Similarly, in Australia, the Chinese artesunate product is available under a Special Access Scheme for those with parasitaemia > 2%, or other features of severe disease. In the US and Canada, a GMP form of artesunate has been developed by the Walter-Read institute as an investigational new drug for use only in those countries.

Although there is no evidence to support the use of adjunctive exchange transfusion in cases of high parasitaemia, the US, Canadian and UK treatment guidelines all suggest that this should be considered for those with parasite counts greater than 10%. Artemisinins kill parasites at all stages of their life cycle and cause the most rapid fall in parasite numbers of all the antimalarial drugs; a drop in parasite numbers of around 10^4 per 48 h for artemisinins, compared to 10^3 for chloroquine and 10^2 for mefloquine and quinine [51]. With the increasing availability of artemisinins, and the rapid falls in parasite counts observed using parenteral artesunate, the theoretical benefits of exchange transfusion are now diminished such that the potential risks probably outweigh the potential benefits. In Australia but not the UK, Canada or US, a single stat dose of primaquine of 45 mg for an adult is given following treatment of falciparum malaria to sterilise gametocytes in the blood and prevent onward transmission by mosquitoes endemic to that country.

For non-falciparum malaria, chloroquine remains the treatment of choice, though artemether-lumefantrine, atovaquone-proguanil, mefloquine and quinine are also effective [21]. Because chloroquine resistance is uncommon, the UK treatment guidelines recommend chloroquine as first-line treatment for vivax and that alternatives should be used only if chloroquine cannot be tolerated or in the event of treatment failure. In the US, atovaquone-proguanil, mefloquine or quinine are recommended for suspected chloroquine-resistant vivax, and in Australia artemether-lumefantrine is the treatment of choice. Primaquine should be given (after G6PD testing) concurrently with chloroquine if possible, to prevent relapse of vivax and ovale infections, and is the only drug currently licensed for this purpose.

Future considerations and summary

The WHO campaign for malaria eradication was abandoned in 1969 in favour of a strategy of malaria control after it became clear that worldwide eradication could not be achieved using the tools available at that time. The cornerstones of malaria control in the tropics today include the prompt provision of effective treatment, the use of long-lasting ITNs, indoor spraying with insecticides, and intermittent presumptive therapy in pregnancy and infants to

prevent or reduce the consequences of infection in these vulnerable groups. The ultimate goal for malaria control is the development of an effective and affordable vaccine. The RTS,S/AS02A and RTS,S/AS01E vaccines, based on antigens found on the surface of sporozoites, have been shown in field studies in Africa to have protective efficacy rates of around 40% against new infections [52, 53]. While these trials are encouraging and partial protection may be of great importance in endemic regions, a wholly protective vaccine for travellers or those living in endemic areas remains many years distant. The continued monitoring for the emergence and spread of drug resistance is vital to guide our choices of drugs for chemoprophylaxis and treatment of malaria in different locations.

Further information for travellers and physicians

Excellent web reference resources are available to the public and health professionals giving country- and disease-specific advice. A selection of these resources is shown below.

UK

National Travel Health Network and Centre (www.nathnac.org)
Travax (www.travax.nhs.uk)

USA

wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria.aspx

References

1. World Health Organisation (2011) World Malaria Report 2011. WHO.
2. Cox-Singh J *et al.* (2008) Plasmodium knowlesi malaria in humans is widely distributed and potentially life threatening. *Clin Infect Dis* **46**(2): 165–171.
3. Sina B (2002) Focus on Plasmodium vivax. *Trends Parasitol* **18**(7): 287–289.
4. Warrell D and Gilles H (2002) *Essential Malariology*, 4th edn. Arnold Publishers, London.
5. Miller LH *et al.* (2002) The pathogenic basis of malaria. *Nature* **415**(6872): 673–679.
6. Drakeley CJ *et al.* (2000) Estimates of the infectious reservoir of Plasmodium falciparum malaria in The Gambia and in Tanzania. *Trans Roy Soc Trop Med Hyg* **94**(5): 472–476.
7. Snow RW *et al.* (1997) Relation between severe malaria morbidity in children and level of Plasmodium falciparum transmission in Africa. *Lancet* **349**(9066): 1650–1654.
8. Snow RW *et al.* (1999) Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. *Bull World Health Org* **77**(8): 624–640.
9. Greenwood B *et al.* (1991) Why do some African children develop severe malaria? *Parasitol Today* **7**(10): 277–281.
10. Lalloo DG *et al.* (2007) UK malaria treatment guidelines. *J Infect* **54**(2): 111–121.
11. Brabin BJ (1983) An analysis of malaria in pregnancy in Africa. *Bull World Health Org* **61**(6): 1005–1016.
12. Slutsker L and Marston BJ (2007) HIV and malaria: interactions and implications. *Curr Opin Infect Dis* **20**(1): 3–10.
13. Ackerman H *et al.* (2005) A comparison of case-control and family-based association methods: the example of sickle-cell and malaria. *Ann Hum Genet* **69**(5): 559–565.
14. Roberts DJ and Williams T (2003) Hemoglobinopathies and resistance to malaria. *Redox Rep* **8**: 304–310.
15. World Health Organixation (2000) Severe falciparum malaria. World Health Organization, Communicable Diseases Cluster. *Trans Roy Soc Trop Med Hyg* **94**(Suppl. 1): S1–90.
16. Enserink M (2008) Malaria. Signs of drug resistance rattle experts, trigger bold plan. *Science* **322**(5909): 1776.
17. Bjorkman A and Bhattarai A (2005) Public health impact of drug resistant Plasmodium falciparum malaria. *Acta Trop* **94**(3): 163–169.
18. Noedl H *et al.* (2008) Evidence of artemisinin-resistant malaria in western Cambodia. *N Engl J Med* **359**(24): 2619–2620.
19. White NJ (2008) Qinghaosu (artemisinin): the price of success. *Science* **320**(5874): 330–334.
20. Pukrittayakamee S. *et al.* (1994) Quinine in severe falciparum malaria: evidence of declining efficacy in Thailand. *Trans Roy Soc Trop Med Hyg* **88**(3): 324–327.
21. Baird JK (2004) Chloroquine resistance in Plasmodium vivax. *Antimicrob Agents Chemother* **48**(11): 4075–4083.
22. Ehrman FC *et al.* (1945) Plasmodium vivax Chesson strain. *Science* **101**(2624): 377.
23. Health Protection Agency (2007) Foreign travel-associated illness in England, Wales and Northern Ireland. Ref Type: Report.
24. Fitzsimmons GJ *et al.* (2009) Arboviral diseases and malaria in Australia, 2007/08: annual report of the National Arbovirus and Malaria Advisory Committee. *Commun Dis Intell* **33**(2): 155–169.
25. Committee to Advise on Tropical Medicine and Travel (2009) Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers. Ref Type: Report.
26. Health Protection Agency (2011) Health Protection Weekly Report – Malaria Data for 2010. Volume 5, number 17.
27. Center for Disease Control and Prevention (2012) Malaria Surveillance – United States, 2010. *MMWR Morb Mortal Wkly Rep: Surveillance Summaries* **61**(2): 1–22.
28. World Tourism Organisation (2010) Tourism 2020 Vision, http://www.unwto.org/facts/eng/vision.htm (accessed 2 May 2010).
29. Kofoed K and Petersen E (2003) The efficacy of chemoprophylaxis against malaria with chloroquine plus proguanil, mefloquine, and atovaquone plus proguanil in travelers from Denmark. *J Travel Med* **10**(3): 150–154.
30. Lalloo DG and Hill DR (2008) Preventing malaria in travellers. *BMJ* **336**(7657): 1362–1366.

31. Chiodini PL *et al.* (2007) Guidelines for malaria prevention in travellers from the United Kingdom. Health Protection Agency.
32. Goodyer LI *et al.* (2010) Expert review of the evidence base for arthropod bite avoidance. *J Travel Med* **17**(3): 182–192.
33. Fradin MS and Day JF (2002) Comparative efficacy of insect repellents against mosquito bites. *N Engl J Med* **347**(1): 13–18.
34. McGready R *et al.* (2001) Safety of the insect repellent N,N-diethyl-M-toluamide (DEET) in pregnancy. *Am J Trop Med Hyg* **65**(4): 285–289.
35. Lengeler C (2000) Insecticide-treated bednets and curtains for preventing malaria. *Cochrane Database Syst Rev* (2): CD000363.
36. Center for Disease Control and Prevention (2010) Health Information for International Travel – Yellow Book, http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria.aspx (accessed 2 May 2012).
37. World Health Organization (2010) *Guidelines for the Treatment of Malaria*. WHO, Geneva.
38. O'Meara WP *et al.* (2008) Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. *Lancet* **372**(9649): 1555–1562.
39. Greenwood B (2009) Can malaria be eliminated? *Trans Roy Soc Trop Med Hyg* **103**(Suppl. 1): S2–S5.
40. Center for Disease Control and Prevention (2011) Malaria Treatment (United States), http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html (accessed 2 May 2012).
41. Centre for Disease Control (2007) Malaria Guidelines for Health Professionals in the Northern Territory, http://www.health.nt.gov.au/library/scripts/objectifyMedia.aspx?file=pdf/10/94.pdf&siteID=1&str_title=Malaria.pdf (accessed 2 May 2012).
42. D'Acremont V *et al.* (2002) Treatment of imported malaria in an ambulatory setting: prospective study. *Br Med J* **324**(7342): 875–877.
43. Melzer M (2006) Outpatient treatment of falciparum malaria is possible. *Br Med J* **333**(7564): 397–398.
44. Newman RD *et al.* (2004) Malaria-related deaths among US travelers, 1963–2001. *Ann Intern Med* **141**(7): 547–555.
45. Muhlberger N *et al.* (2003) Age as a risk factor for severe manifestations and fatal outcome of falciparum malaria in European patients: observations from TropNetEurop and SIMPID Surveillance Data. *Clin Infect Dis* **36**(8): 990–995.
46. Moore DA *et al.* (2003) Assessing the severity of malaria. *Br Med J* **326**(7393): 808–809.
47. Bunn A *et al.* (2004) Falciparum malaria in malaria-naive travellers and African visitors. *QJM*, **97**(10), 645–649.
48. Ranque, S. *et al.* (2005) Treatment of imported malaria in adults: a multicentre study in France. *Q J Med* **98**(10): 737–743.
49. Dondorp A *et al.* (2005) Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* **366**(9487): 717–725.
50. Dondorp AM *et al.* (2010) Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* **376**(9753): 1647–1657.
51. White NJ (1997) Assessment of the pharmacodynamic properties of antimalarial drugs in vivo. *Antimicrob Agents Chemother* **41**(7): 1413–1422.
52. Abdulla S *et al.* (2008) Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. *N Engl J Med* **359**(24): 2533–2544.
53. Bejon P *et al.* (2008) Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age. *N Engl J Med* **359**(24): 2521–2532.

MALARIA CHEMOPROPHYLAXIS

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Prevention of falciparum malaria, with its potential to cause severe malaria and death, is the primary aim of malaria chemoprophylaxis. A key determinant of malaria chemoprophylaxis is therefore the risk of *P. falciparum* infection and the profile of drug resistance in the geographical area to be visited. Since species of malaria parasites, other than *P. falciparum*, are sensitive to all forms of malaria chemoprophylaxis, with the exception of chloroquine-resistant *P. vivax* in Papua New Guinea and Indonesia (and the hypnozoite forms of *P. vivax* and *ovale*), malaria chemoprophylaxis regimens chosen to cover *P. falciparum* will also prevent primary infection with other malarial species. The risk of malaria transmission varies greatly between endemic areas and is usually factored into the country-by-country guidelines issued by many national and international bodies. However, the key principle is that although guidelines exist, they are only published periodically and risk assessments can change, therefore reference should be made to reliable, up-to-date information such as online resources available at www.cdc.gov/travel, www.nathnac.org, www.who.int/ith/en/.

There is now widespread resistance to chloroquine in most falciparum-endemic countries (see Figures 10.2 and 10.3), and international guidelines from WHO and national authorities such as the UK, US and Canada [1] all recommend a choice of three priority regimens for adults travelling to areas with significant levels of resistance: atovaquone/proguanil (available as a fixed combination Malarone), mefloquine or doxycycline, which are generally considered to be equally effective except in areas of multi-druug resistance. Mefloquine resistance is present in western Cambodia, eastern Burma and areas of Thailand bordering these countries, with scattered pockets of resistance reported also from the Amazon basin in South America; atovaquone/proguanil or doxycycline are therefore recommended for travel to these areas. In the few remaining areas of the world where chloroquine resistance is not seen, including mainly the Caribbean and some Middle Eastern countries, chloroquine

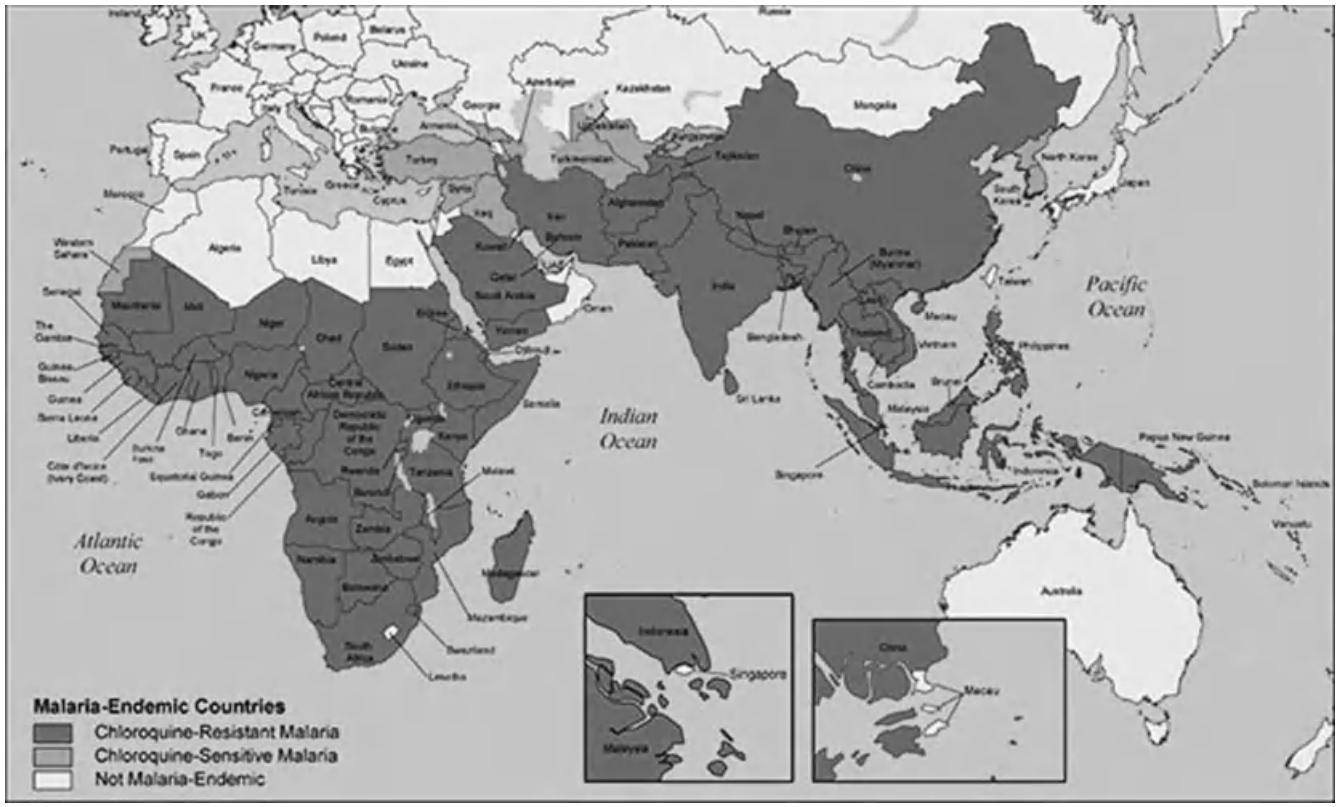

Figure 10.2 Presence of chloroquine resistance in malaria-endemic countries: Asia and Africa.
From www.cdc.gov (updated 2 July 2010) http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria.aspx#990]

alone can be used, and where the prevalence of chloroquine resistance is low to moderate, chloroquine plus proguanil is an option recommended by UK and WHO guidelines [2]. In the US, hydroxychloroquine, a 4-aminoquinoline similar to chloroquine, is recommended by the CDC as an alternative malaria prophylaxis in areas with chloroquine-sensitive *P. falciparum*. Atovaquone/proguanil and doxycycline are generally not recommended in pregnancy, the latter also in young children, and more information on chemoprophylaxis in special groups including children is given later in the chapter.

Randomised controlled trials give efficacy rates for the prevention of *P. falciparum* of 95–100% for mefloquine [3], doxycycline [3, 4] and atovaquone-proguanil respectively [5–7]. However, extrapolation from trials can be difficult because the risk of transmission of *P. falciparum* varies between locations, and many trials involved military personnel who are healthier, on fewer medications and may have better adherence than the general population. In the real world, adherence is a significant limiting factor to effectiveness, and the medical history of the traveller and the side effect profile of each option will be decisive factors in the choice of malaria chemoprophylaxis regimen. This is presented in summary form in Table 10.4.

A randomised controlled trial comparing tolerability in travellers using one of four malaria chemoprophylaxis regimens found the frequency of adverse events requiring medical advice to be 12% with chloroquine-proguanil, 11% with mefloquine, 7% with atovaquone-proguanil and 6% with doxycycline [8]. A Cochrane review [9] of 4,280 people enrolled in eight controlled trials reported similar findings with atovaquone-proguanil and doxycycline adverse events emerging as the best-tolerated regimens.

Given the potential adverse events and financial costs of malaria chemoprophylaxis, the traveller's risk of exposure to malaria should be considered when travelling to lower-risk countries. Malaria transmission may vary significantly within endemic countries, often concentrated in focal rural areas away from tourist destinations. Detailed maps are available at online resources for consultation alongside the traveller's itinerary. Transmission risk may also be affected by time of year, being higher in humid conditions, rural rather than urban areas, and in backpacker's hostels compared with air-conditioned hotels. In very low-transmission

Figure 10.3 Presence of chloroquine resistance in malaria endemic countries: Americas.

countries, awareness of malaria risk and symptoms, knowing when to seek medical attention and bite avoidance are recommended rather than chemoprophylaxis. Sub-Saharan Africa, however, is an exception where the risk of malaria should be considered as high except in defined areas of seasonal transmission in Southern Africa.

When prescribing a malaria chemoprophylaxis regimen, it is usual to start it at least a week prior to arrival in the endemic area (or 2–3 weeks for mefloquine if a trial dose period is indicated). If the traveller knows they tolerate a drug, then starting 1–2 days before arrival is sufficient time for daily regimens to achieve effective levels, and 1 week before arrival for weekly mefloquine or chloroquine/hydroxychloroquine. It is very important that doses are not missed, and that travellers take their medication with them rather than buying it while abroad, where the optimal regimen may not be available and drugs may be counterfeit. Finally, chemoprophylaxis should always be considered as only one part of the ABCD – awareness, bite avoidance, chemoprophylaxis, diagnosis – approach to prevention.

Mefloquine

Mefloquine, although tolerated by the majority of users, has a notable profile of neuropsychiatric adverse events, ranging from sleep disturbances such as vivid dreams and insomnia to, rarely, seizures and psychosis, particularly depression. Several reviews have synthesised the data from a large number of mefloquine studies with varying designs and definitions, and sometimes conflicting results [10–12]. The milder neuropsychiatric symptoms occur in 9–57% of users, depending on study definitions and design, although these rates are often comparable to those of chloroquine and proguanil. Neuropsychiatric adverse events are significantly more frequent in women. Serious events requiring hospitalisation are rare with mefloquine and are estimated to occur at a frequency ranging from 1 in 607 to 1 in 20,000 (most large epidemiological studies found an incidence of 1/10,000 users). Some experts recommend that mefloquine should not be administered to airline pilots (the UK Civil Aviation Authority), and use of mefloquine is an exclusion criteria for scuba diving in some centres, although a comprehensive review of this topic found no evidence in the literature to support this ban [10]. Other exclusion criteria include those who have a history of severe liver disease, psychiatric illness, depression, epilepsy or a family history of epilepsy. Caution should be exercised when considering mefloquine for those with hepatic disease as mefloquine is excreted exclusively through the liver and can therefore accumulate rapidly in moderate or severe liver failure.

Mefloquine can be recommended for pregnant women who travel to areas of chloroquine-resistant *P. falciparum* when travel cannot be deferred. A new drug safety database analysis shows that fetal loss and birth prevalence of malaformations (4.39%) in mefloquine exposed mothers were comparable to background levels in the general population [13]. Authorities worldwide vary in their recommendations as reviewed recently [12] and many experts recommend a 'risk-benefit' analysis before prescribing mefloquine for pregnant women. The UK, WHO, Swiss expert groups on malaria prophylaxis and the manufacturer are restrictive with respect to mefloquine use during pregnancy, particularly in the first trimester. The US and Canadian guidelines now allow the use of mefloquine in all trimesters and the American and Canadian advice does not specify the need to avoid pregnancy for three months post-exposure to

Table 10.4 Malaria chemoprophylaxis

Drug	Action	Adult dosage	Pregnancy	Main contraindications	Adverse events	Drug interactions
Atovaquone/ proguanil	Inhibits mitochondria	One tablet 250 mg atovaquone/100 mg proguanil) daily Start 1–2 days before travel, and continue for 7 days after travel	No data, not recommended	Hypersensitivity to atovaquone or proguanil Severe renal impairment (creatinine clearance <30 ml/ min) Breast-feeding (no data, not recommended)	Headache Gastrointestinal upset	Atovaquone levels reduced by rifampicin, tetracycline, metoclopromide. May interact with indinavir, zidovudine
Doxycycline	Inhibits protein synthesis	100 mg daily Start 1–2 days before travel, and continue for 4 weeks after travel	Contraindicated	Allergy to tetracyclines Liver impairment/ hepatotoxic drugs SLE, myasthenia gravis	Gastrointestinal upset common (take with plenty of water), rarely oesophageal ulcers Photoallergic skin rash – high protection sun screen should be worn Vaginal thrush	Warfarin and cyclosporin levels may be increased May reduce effectiveness of oral typhoid vaccine
Mefloquine	Uncertain	One 250 mg tablet weekly Start 1 week before travel (for first time user: 2–3 weeks before) and continue for 4 weeks after travel	Safe	Depression, history of psychosis Epilepsy	Common – dizziness, headache, vivid dreams, insomnia, mood alteration Rare – seizures, psychosis	Antagonises antiepileptics Several antiarrythmics Quinine (do not give mefloquine within 12 h of quinine)
Chloroquine (resistance widespread)	Interferes with pigment formation > toxic products	300 mg base (two tablets) weekly Start 1 week before travel and continue for 4 weeks after travel	Safe	Epilepsy Psoriasis (may exacerbate) Myasthenia gravis	Gastrointestinal upset Headache	Increased risk of arrhythmias and toxicity with amiodarone, digoxin, Ciclospirin, mefloquine
Proguanil (strains are rarely fully sensitive, only used in combination)	Interferes with folic acid synthesis	200 mg (two tablets) daily Start 1 2 days before travel, and continue for 4 weeks after travel	Folic acid supplements required	Allergy to proguanil Renal impairment	Gastrointestinal upset Occasionally mouth ulcers	May enhance warfarin

Adapted from NaTHNaC 'Yellow Book' 2012 edition

mefloquine. Mefloquine should be taken as a single weekly dose, starting 1 week before departure for those who have tolerated mefloquine previously, continued throughout the risk of exposure and for 4 weeks upon return. Those who have never taken mefloquine previously should start 2–3 weeks in advance of departure to check tolerability and if necessary to allow for a switch to an alternative type of malaria chemoprophylaxis in advance of travel. Mefloquine is licensed for use continuously for up to 1 year and data suggest that it can be prescribed safely for up to 3 years continuously. The drug is a good and affordable option for long-term travellers.

Doxycyline

Doxycycline is reputed to cause photosensitive rashes and should be avoided in those who are fair-skinned, and being a broad-spectrum antibiotic it can predispose to thrush, although it has the advantage of preventing rickettsial infection. Doxycycline is available as hyclate and monohydrate salts and preference should be given to doxycycline monohydrate as it is associated with fewer gastrointestinal adverse events than the hyclate form but is more expensive [14, 15]. It should be taken with plenty of water and importantly one should not lie down for an hour after taking it, to reduce the risk of dyspepsia and oesophageal ulceration. Consideration should be given to the use of concomitant medication; the absorption of doxycycline may be impaired by concurrently administered antacids containing aluminium, calcium, magnesium or other drugs containing these cations; oral zinc, iron salts or bismuth preparations. The serum half-life of doxycycline may be shortened with anti-epileptics, e.g. barbiturates, carbamazepine or phenytoin. Doxycycline may also increase the plasma concentration of cyclosporine and co-administration should only be undertaken with appropriate monitoring. Doxycyline is generally contraindicated in pregnancy and trying to conceive is to be avoided until 1 week has elapsed since the completion of a course. Recent guidance provided by the Royal College of Obstetricians and Gynaecologists [16] advises that female travellers prescribed the oral contraceptive pill are no longer required to use additional methods of contraception while prescribed doxycycline concurrently as doxycycline is classed as a non-enzyme-inducing antibiotic. Female travellers should be advised that the use of additional methods of contraception does apply if vomiting or diarrhoea were to occur. Absorption of doxycycline may be reduced by diarrhoea and vomiting and if a dose is inadvertently omitted or vomiting occurs within 1 hour of taking doxycycline, another dose should be taken and the course completed. In the event of diarrhoea occurring, the course of doxcycline should continue uninterrupted.

Doxycycline is also contraindicated in those who are breast-feeding, with systemic lupus erythematosis or porphyria, and children under 12 years (children under 8 years old in North America) because of possible permanent tooth discoloration and/or delayed bone development. Caution should be exercised when considering doxycycline for those with hepatic disease, as doxycycline is excreted exclusively through the liver and can therefore accumulate rapidly in moderate or severe liver failure. As malaria chemoprophylaxis, doxycyline is taken as a single 100 mg dose daily, starting 1 or 2 days before departure, continued throughout the risk of exposure and for 4 weeks upon return. As tetracyclines are used for other indications (treatment of acne) for long periods of time of up to 2 years, it is felt that doxycyline may be used safely as malaria chemoprophylaxis similarly. The use of doxycycline as an antimalarial has been recently reviewed in detail [17].

Atovaquone-proguanil

Overall, atovaquone-proguanil appears to be the best tolerated of currently recommended malaria chemoprophylaxis [11]. It has the additional advantage that it acts on malaria parasites at the liver schizont stage, termed 'causal' prophylaxis. It can therefore be stopped soon (1 week) after leaving a malarious area, whereas the other drug regimes act only on the blood parasite stage ('suppressive' prophylaxis) and must be continued for 4 weeks after leaving the endemic area, which can reduce full adherence. Atovaquone-proguanil, a tablet containing 250 mg atovaquone plus 100 mg proguanil, is taken as a single dose daily, starting 1 day before departure, continued throughout the risk of exposure and for 7 days upon return. It is licensed as a paediatric formulation containing 62.5 mg atovaquone and 25 mg proguanil, for children who weigh more than 11 kg and may be considered for 'off-licence' prescribing in infants who weigh 5 to <11 kg, The Centre for Disease Control advise the following prescription of paediatric atovaquone-proguanil:

- for infants weighing 5–8 kg half a paediatric tablet daily
- for those weighing >8–10 kg three-quarters of a paediatric tablet daily
- for those weighing >10–20 kg one paediatric tablet daily.

Atovaquone-proguanil is licensed to be prescribed for up to 28 days and there are limited data to support its continuous use safely for at least 1 year. Adverse events with atovaquone-proguanil are uncommon as it is a well-tolerated drug; a change in sleep pattern, coughing and mouth ulcers have been reported. Absorption of atovaquone-proguanil may be reduced by diarrhoea and vomiting and if a dose is inadvertently omitted or vomiting occurs within 1 hour of taking atovaquone-proguanil, another dose should be taken and the course completed. In the event of diarrhoea

occurring, the course of atovaquone-proguanil should continue uninterrupted. Consideration should be given to the use of concomitant medication; the absorption of atovaquone-proguanil may be impaired by concurrently administered tetracyclines, metoclopramide, rifampicin, rifabutin or indinavir preparations. Caution should be exercised when considering atovaquone-proguanil for those with renal disease because of the metabolism of proguanil. Similarly, proguanil may interact with warfarin and may prolong its anticoagulant effect. It is recommended that the prothrombin time be checked prior to departure and upon return; long trips may necessitate monitoring the prothrombin time while abroad. Atovaquone-proguanil is currently not recommended in pregnancy due to a lack of data, and breast-feeding (of babies < 5 kg) and trying to conceive is to be avoided until 2 weeks have elapsed since the completion of a course.

Chloroquine

Chloroquine, alone or in combination with proguanil, is indicated as malaria chemoprophylaxis in the few remaining areas of the world where chloroquine resistance is not seen, including mainly the Caribbean and some Middle Eastern countries. Where the prevalence of chloroquine resistance is low to moderate, chloroquine plus proguanil is an option recommended by UK and WHO guidelines [2], but not in the US for those travelling to the Indian subcontinent.

Chloroquine is frequently associated with nausea and diarrhoea, with other less common adverse events of skin rashes, blurred vision, alopecia, dizziness, mood change, photosensitivity or seizures. Consideration should be given to the use of concomitant medication; the absorption of chloroquine may be reduced by concurrently administered antacids and it is recommended that antacids should be taken at least 2 hours before or after taking chloroquine. Chloroquine is known to exacerbate psoriasis and very occasionally its use is associated with seizures. Chloroquine is contraindicated in those with epilepsy or in those with a family history of a first-degree relative with a history of idiopathic epilepsy. Caution should be exercised when considering the prescribing of chloroquine for those with hepatic or renal disease as chloroquine. Similarly, irreversible retinal damage and corneal changes may develop when chloroquine has been prescribed at continuous high doses for longer than 12 months or as weekly prophylaxis for longer than 3 years and after it has been discontinued. Ophthalmic examination prior to and at 3- to 6-monthly intervals during use is required for those prescribed chloroquine on this basis.

As a malaria chemoprophylaxis, chloroquine is taken in the form of two tablets once a week, on the same day each week, starting 1 week before departure, continued throughout the risk of exposure and for 4 weeks upon return. In some European countries a fixed combination of chloroquine and proguanil is available for daily intake. In the US, hydroxychloroquine rather than chloroquine may be recommended as a chemoprophylaxis for travellers to areas of chloroquine sensitive *P. falciparum*.For those travellers who may have been prescribed hydroxychloroquine 200–400 mg daily for the treatment of an underlying medical condition such as rheumatoid arthritis or lupus erythematosus, and for whom chloroquine or chloroquine plus proguanil is indicated, hydroxychloroquine may also be used as malaria prophylaxis. Usefully, chloroquine is available in syrup form for infants and children and as there are decades of experience with the use of chloroquine, it is understood to be safe to be prescribed during pregnancy and while breast-feeding.

Proguanil

It is not uncommon for adverse events such as anorexia, nausea and mouth ulcers to be associated with the use of proguanil; less common are those of diarrhoea, constipation and skin rashes. Caution should be exercised when considering prescribing proguanil for those with renal disease because of the metabolism of proguanil. Similarly, proguanil may interact with warfarin and may prolong its anticoagulant effect. It is recommended that the prothrombin time be checked prior to departure and upon return; long trips may necessitate monitoring the prothrombin time while abroad.

As malaria chemoprophylaxis, proguanil is taken in the form of two tablets once daily, starting 1 week before departure, continued throughout the risk of exposure and for 4 weeks upon return. As with chloroquine, proguanil has been prescribed for more than 40 years and it is understood to be safe to be prescribed during pregnancy, although folate supplements are advised because proguanil does exhibit antifolate activity by interfering with the folic-folinic acid systems. Proguanil is similarly safe to prescribe while breast-feeding and may be prescribed continuously for a period of at least 5 years.

Proguanil is usually prescribed in combination as malaria chemoprophylaxis and the above apply to the prescribing of these drugs alone or in combination.

Malaria prophylaxis: *Plasmodium vivax* and *Plasmodium ovale*

P. vivax and *P. ovale* present a unique challenge for malaria prophylaxis: during the liver stage of infection, some sporozoites develop into latent forms called hypnozoites. Hypnozoites lay dormant in the liver and can reactivate after weeks,

months or even years to cause new blood-stage infection [18, 19]. Reactivation patterns are poorly understood, but may relate to sporozoite inoculum and strain geographic origin [20, 21]. Blood schizonticides used for prophylaxis can prevent clinical episodes of *P. vivax* and *P. ovale*; however, they do not prevent hypnozoite development and relapses can occur after termination of prophylaxis. The potentially long delay between travel period and relapse, as well as the lower parasitaemias associated with these species, may impede prompt diagnosis. Moreover, there is mounting evidence that *P. vivax*, particularly in Papua New Guinea, may be associated with severe disease and death [22–24]. Thus, prophylaxis for travellers to *P. vivax*- and *P. ovale*-endemic areas would ideally target hypnozoites to avoid future relapses.

Primaquine

Currently, primaquine is the only approved drug that targets hypnozoites. This 8-aminoquinoline also has activity against developing liver-stage parasites and gametocytes of all Plasmodium species and some activity against *P. vivax* blood-stage parasites [25, 26]. Primaquine has a short plasma half-life (4–6 h). Its mechanism of action remains unclear, although biotransformation appears to be required for its activity [27]. Primaquine metabolites may kill parasites by generating oxidative stress, impairing parasite mitochondrial function [28, 29] or inhibiting heme polymerization [30].

Primaquine is currently in use for the following indications.

1 Presumptive anti-relapse therapy (PART). Travellers who were intensely exposed to *P. vivax* or *P. ovale* can be treated upon return with primaquine for 14 days to eliminate hypnozoites that may be present in the liver. The recommended dose has been increased from 15 to 30 mg base/day [31, 32], due to primaquine-tolerant *P. vivax* strains [33, 34]. Total dose can be increased to 6 mg/kg in individuals >70 kg, since under-dosing in this group has been associated with higher risk of *P. vivax* relapse [30, 35]. Primaquine administration should overlap with the final 2 weeks of the prophylactic blood schizonticide (the final week for atovaquone-proguanil), as older studies reported chloroquine-primaquine synergy in eliminating hypnozoites [36]. With full compliance, this regimen is highly effective (>95%) [31]. Most guidelines recommend PART only for long-term visitors to endemic areas (e.g. missionaries, volunteers) or travel to areas with very high risk of infection (e.g Omo river, Ethiopia) [38].

2 Radical cure. Clinical *P. vivax* or *P. ovale* infection can be treated with primaquine in addition to a blood schizonticide to prevent future relapses. Recommended dosing is as above. If possible, the course of primaquine should overlap with the blood schizonticide. Recent meta-analyses found this use of primaquine to be effective in preventing *P. vivax* relapse [35, 38], although there are few well-designed trials in the literature. If travel was to an area with chloroquine-resistant *P. vivax* [39], other drugs such as artemisinin derivatives can be used with primaquine [40, 41], although these combinations require additional investigation [34].

3 Primary prophylaxis. A number of studies support the safety, tolerability and short-term efficacy (85–93%) of primaquine as primary causal prophylaxis for *P. vivax* and *P. falciparum* [26, 42–45]. Primaquine has not been licensed for this indication [33]. However, some authorities now recommend off-label use of primaquine as a second-line option for primary prophylaxis in individuals with normal levels of glucose-6-phosphate-dehydrogenase (G6PD), if other chemoprophylactic regimens are inappropriate or contraindicated [31, 46], if travellers are undertaking brief trips, or if travel is to a *P. vivax*-dominated area [10, 26]. The recommended regimen is 30 mg base/day, from 1 day prior to travel until 7 days following return. The short post-travel regimen compared with blood schizonticides may increase compliance. However, further studies should address long-term efficacy, and there are some concerns regarding development of primaquine resistance [47].

If travellers to *P. vivax* or *P. ovale*-endemic regions do not take primaquine as primary prophylaxis or PART, they must be educated about the possibility of relapsing malaria and advised to seek medical attention if they develop malaria symptoms following travel.

Primaquine toxicity

Primaquine can cause adverse gastrointestinal events, but symptoms are generally mild or moderate if taken with food [48]. Primaquine can induce transient methemoglobinemia; however, most cases are mild and self-resolving, and none has been symptomatic. Two per cent of individuals have severe reactions to primaquine [31].

Importantly, primaquine can cause life-threatening haemolysis in individuals with G6PD deficiency, presumably due to the inability of erythrocytes to neutralise primaquine-induced oxidative stress. Haemolysis is less severe for individuals with the A variant (typically of African descent) who have relatively mild deficiencies. Mediterranean and Asian variants have minimal enzyme activity and are at high risk of severe haemolysis [49]. G6PD testing must always be performed prior to administering primaquine and G6PD-deficient individuals should not be given primaquine. Some guidelines indicate that after appropriate risk-benefit analysis, infected people with mild G6PD deficiency may receive weekly primaquine with careful monitoring [32, 40].

Primaquine should not be used in women who are pregnant or planning pregnancy, as the G6PD status of the fetus is unknown. Breast-feeding women should receive primaquine only if the G6PD status of the child is normal. Primaquine is also contraindicated in persons taking other drugs that promote haemolysis [40].

Future treatments targeting hypnozoites

Novel anti-hypnozoite drugs – ideally safe for use in G6PD deficiency – are needed. Drug discovery is hindered by a poor understanding of hypozoite biology [50] and primaquine mechanism of action. Research efforts mainly focus on primaquine analogues [24].

Tafenoquine is an 8-aminoquinolone co-developed by the Walter Reed Army Institute of Research and GlaxoSmithKline. It has activity against hypnozoites, liver- and blood-stage parasites, sporozoites and oocyst development in the mosquito [51–54]. Phase I/II trials have demonstrated good safety and tolerability. Like primaquine, tafenoquine induces asymptomatic methaemoglobinaemia and mild/moderate gastrointestinal problems, with few severe effects documented [55]. However, tafenoquine causes haemolysis in G6PD-deficient individuals [56]. Tafenoquine has been shown to be efficacious (85–100%) when used for causal prophylaxis of *P. vivax* or *P. falciparum* [56–59], PART [60], or radical cure of *P. vivax* in combination with chloroquine or artesunate [61–63]. A major advantage of tafenoquine over primaquine is its long half-life (14 days [64], which permits shorter regimens and thus increased compliance. Prophylactic regimens have included a 3-day loading period or a loading dose followed by weekly or monthly dosing, and radical cure can be achieved in 1–3 days. In a recent Phase III trial of Australian soldiers, a weekly dose of tafenoquine was as effective as mefloquine in preventing Plasmodium infection for 6 months after return from an endemic area, without a need for post-exposure dosing [64]. Further testing is required in civilian travellers and children, although contraindication in G6PD deficiency is a major drawback for this drug.

Bulaquine is a primaquine pro-drug developed by the Central Drug Research Institute in India that has similar activity to primaquine [66, 67]. A double-blind randomised trial for radical cure of *P. vivax* demonstrated a comparable but marginal decrease in 1-year relapse rates for bulaquine and primaquine compared with placebo [68]. However, the primaquine regimen used in this study was suboptimal [35, 38] and further optimisation of bulaquine regimens is needed. A Thai study comparing 7-day regimens of primaquine or bulaquine for treatment of *P. vivax* demonstrated good tolerability, although relapse prevention was not assessed [69]. This study also evaluated a small group of G6PD-deficient subjects, and found that daily bulaquine induced significantly less haemolysis than weekly primaquine.

Malaria prophylaxis: *Plasmodium malariae*

Drug resistance is not a concern with this uncommon (though widely distributed) cause of malaria, so regimens designed for prevention of *P. falciparum* will be effective against *P. malariae*.

Malaria prophylaxis: *Plasmodium knowlesi*

P. knowlesi is a primate malaria of long- and pig-tailed macaque monkeys which is capable of causing zoonotic infections. The morphology of the parasite on blood films can resemble ring forms of *P. falciparum*, or more often looks indistinguishable from *P. malariae*, and it has now been recognised that large-scale human infection, misdiagnosed as *P. malariae*, occurs in certain areas of Southeast Asia [70], particularly Malaysian Borneo. Recent studies have found that most cases of suspected *P. malariae* in Sarawak and Sabah were in fact *P. knowlesi* when tested by polymerase chain reaction (PCR); it accounted for 27% of reported malaria cases from 12 hospitals in central Sarawak during 2001–06 [71], and up to 70% in the Kapit region [72]. The parasite is restricted to the *Anopheles leucosphyrus* mosquito group, which live at the forest fringes and are equally attracted to humans and monkeys. Consequently most infections have been found in local tribal populations, but human cases of *P. knowlesi* have also been diagnosed in areas of peninsular Malaysia, southern Thailand, the China-Myanmar border and the Phillipines, and there have been case reports of infections in western travellers returning from these areas [73, 74].

P. knowlesi is capable of causing a spectrum of disease severity in humans, including life-threatening illness that is similar to severe falciparum malaria, and its short asexual cycle of just 24 h can result in high parasite counts and rapid deterioration. The extent of subclinical or benign infection in endemic areas is as yet unknown, as is the optimal chemotherapy. Uncomplicated cases have been successfully treated with chloroquine, and severe cases with IV quinine or artesunate [72], the latter probably producing more rapid resolution [75]. It is therefore likely that the usual chemoprophylaxis regimens for these areas, aimed at preventing *P. falciparum* and *P. vivax*, will also be effective against *P. knowlesi*.

References

1. Chiodini P *et al.* (2007) *Guidelines for Malaria Prevention in Travellers from the United Kingdom*. Health Protection Agency, London.
2. World Health Organization (2011) *Guidelines for the Treatment of Malaria*, second edn. World Health Organization, Geneva.
3. Ohrt C *et al.* (1997) Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* **126**: 963–972.
4. Taylor WR *et al.* (1999) Malaria prophylaxis using azithromycin: a double-blind, placebo-controlled trial in Irian Jaya, Indonesia. *Clin Infect Dis* **28:** 74–81.
5. Nakato H *et al.* (2007) A systematic review and meta-analysis of the effectiveness and safety of atovaquone–proguanil (Malarone) for chemoprophylaxis against malaria. *J Antimicrob Chemother* **60:** 929–936.
6. Sukwa TY *et al.* (1999) A randomized double-blind, placebo-controlled field trial to determine the efficacy and safety of Malarone (atovaquone/proguanil) for the prophylaxis of malaria in Zambia. *Am J Trop Med Hyg* **60**(4): 521–525.
7. Ling J *et al.* (2002) Randomized, placebo-controlled trial of atovaquone/proguanil for the prevention of Plasmodium falciparum or Plasmodium vivax malaria among migrants to Papua, Indonesia. *Clin Infect Dis* **35:** 825–833.
8. Schlagenhauf P *et al.* (2003) Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. *Br Med J* **327**(7423): 1078.
9. Jacquerioz FA and Croft AM (2009) Drugs for preventing malaria in travellers. *Cochrane Database Syst Rev* (4): CD006491. doi: 10.1002/14651858.CD006491.pub2
10. Chen LH *et al.* (2007) Controversies and misconceptions in malaria chemoprophylaxis for travelers. *JAMA: J Am Med Assoc* **297**(20): 2251–2263.
11. Croft AM (2007) Malaria: prevention in travellers. *Clin Evid (Online)* **2007:** pii: 0903.
12. Schlagenhauf P *et al.* (2010) The position of mefloquine as a 21st century malaria chemoprophylaxis – a reveiw. *Malar J* **9:** 357.
13. Schlagenhauf P *et al.* (2010) Pregnancy and fetal outcomes after exposure to mefloquine in the pre- and periconception period and during pregnancy. *Clin Infect Dis* **54:** 124–131.
14. Baudon D *et al.* (1999) Efficacy of daily antimalarial chemoprophylaxis in tropical Africa using either doxycycline or chloroquine-proguanil; a study conducted in 1996 in the French Army. *Trans R Soc Trop Med Hyg* **93:** 302–303.
15. Pagès F *et al.* (2002) Tolerability of doxycycline monohydrate salt vs. chloroquine-proguanil in malaria chemoprophylaxis. *Trop Med Int Health* **7:** 919–924.
16. Faculty of Sexual &Reproductive Healthcare (2011) Clinical Guidance Drug Interactions with Hormonal Contraception. Clinical Effectiveness Unit. Royal College of Obstetricans and Gyanecologists, London, UK. January 2011. ISSN 1755-103X.
17. Tan KR *et al.* (2011) Doxycycline for malaria chemoprophylaxis and treatment: report from the CDC expert meeting on malaria chemoprophylaxis. *Am J Trop Med Hyg* **84:** 517–531.
18. Cogswell FB (1992) The hypnozoite and relapse in primate malaria. *Clin Microbiol Rev* **5:** 26–35.
19. Marty P *et al.* (1987) Anemic Plasmodium ovale malaria after 45 months' incubation. *Presse Med* **16**: 357.
20. Baird JK and Hoffman SL (2004) Primaquine therapy for malaria. *Clin Infect Dis* **39:** 1336–1345.
21. Shute PG *et al.* (1976) A strain of *Plasmodium vivax* characterized by prolonged incubation: the effect of numbers of sporozoites on the length of the prepatent period. *Trans R Soc Trop Med Hyg* **70:** 474–481.
22. Kochar DK *et al.* (2009) Severe *Plasmodium vivax* malaria: a report on serial cases from Bikaner in northwestern India. *Am J Trop Med Hyg* **80:** 194–198.
23. Tjitra E *et al.* (2008) Multidrug-resistant *Plasmodium vivax* associated with severe and fatal malaria: a prospective study in Papua, Indonesia. *PLoS Med* **5**: e128.
24. Price RN *et al.* (2009) New developments in *Plasmodium vivax* malaria: severe disease and the rise of chloroquine resistance. *Curr Opin Infect Dis* **22:** 430–435.
25. Pukrittayakamee S *et al.* (1994) Blood stage antimalarial efficacy of primaquine in *Plasmodium vivax* malaria. *J Infect Dis* **169**: 932–935.
26. Baird JK *et al.* (2003) Primaquine for prevention of malaria in travelers. *Clin Infect Dis* **37:** 1659–1667.
27. Tekwani BL and Walker LA (2006) 8-Aminoquinolines: future role as antiprotozoal drugs. *Curr Opin Infect Dis* **19:** 623–631.
28. Beaudoin RL and Aikawa M (1968) Primaquine-induced changes in morphology of exoerythrocytic stages of malaria. *Science* **160:** 1233–1234.
29. Lanners HN (1991) Effect of the 8-aminoquinoline primaquine on culture-derived gametocytes of the malaria parasite *Plasmodium falciparum*. *Parasitol Res* **77:** 478–481.
30. Vennerstrom JL *et al.* (1999) 8-Aminoquinolines active against blood stage Plasmodium falciparum in vitro inhibit hematin polymerization. *Antimicrob Agents Chemother* **43:** 598–602.
31. Hill DR *et al.* (2006) Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. *Am J Trop Med Hyg* **75:** 402–415.
32. Lalloo DG *et al.* (2007) UK malaria treatment guidelines. *J Infect* **54:** 111–121.
33. Elliott JH *et al.* (2004) Imported *Plasmodium vivax* malaria: demographic and clinical features in nonimmune travelers. *J Travel Med* **11:** 213–217.
34. Baird JK (2009) Resistance to therapies for infection by *Plasmodium vivax*. *Clin Microbiol Rev* **22:** 508–534.
35. Goller JL *et al.* (2007) Regional differences in the response of *Plasmodium vivax* malaria to primaquine as anti-relapse therapy. *Am J Trop Med Hyg* **76:** 203–207.
36. Alving AS *et al.* (1955) Potentiation of the curative action of primaquine in vivax malaria by quinine and chloroquine. *J Lab Clin Med* **46:** 301–306.
37. Schwartz E and Regev-Yochay G (1999) Primaquine as prophylaxis for malaria for nonimmune travelers: a comparison with mefloquine and doxycycline. *Clin Infect Dis* **29:** 1502–1506.

38. Galappaththy GN *et al.* (2007) Primaquine for preventing relapses in people with *Plasmodium vivax* malaria. *Cochrane Database Syst Rev* (24), CD004389.
39. Arguin PM and Soja M (2012) Infectious diseases related to travel. Malaria. In: Brunette GW (ed.), *CDC Health Information for International Travel, Yellow Book*, http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/malaria.htm (accessed 13 August 2012)
40. International Travel and Health (2012) World Health Organization, Geneva, pp 204–235 http://www.who.int/ith/chapters/it2012en_countrylist.pdf (accessed 13 August 2012).
41. Krudsood S *et al.* (2008) High-dose primaquine regimens against relapse of *Plasmodium vivax* malaria. *Am J Trop Med Hyg* **78**: 736–740.
42. Soto J *et al.* (1998) Primaquine prophylaxis against malaria in nonimmune Colombian soldiers: efficacy and toxicity. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* **129:** 241–244.
43. Fryauff DJ *et al.* (1995) Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. *Lancet* **346**: 1190–1193.
44. Weiss WR *et al.* (1995) Daily primaquine is effective for prophylaxis against falciparum malaria in Kenya: comparison with mefloquine, doxycycline, and chloroquine plus proguanil. *J Infect Dis* **171**: 1569–1575.
45. Baird JK *et al.* (2001) Randomized, parallel placebo-controlled trial of primaquine for malaria prophylaxis in Papua, Indonesia. *Clin Infect Dis* **33**: 1990–1997.
46. Public Health Agency of Canada (2009) Drugs for the Prevention and Treatment of Malaria. Supplement: Canadian Recommendations for the Prevention and Treatment of Malaria among International Travellers. *Canadian Communicable Disease Report. Vol. 35*. Public Health Agency of Canada, Ottawa, http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s1/index-eng.php (accessed 13 August 2012).
47. Schlagenhauf P and Petersen E (2008) Malaria chemoprophylaxis: strategies for risk groups. *Clin Microbiol Rev* **21**: 466–472.
48. Clayman CB *et al.* (1952) Toxicity of primaquine in Caucasians. *JAMA: J Am Med Assoc* **149**: 1563–1568.
49. Beutler E and Duparc S (2007) Glucose-6-phosphate dehydrogenase deficiency and antimalarial drug development. *Am J Trop Med Hyg* **77**: 779–789.
50. Mazier D *et al.* (2009) A pre-emptive strike against malaria's stealthy hepatic forms. *Nat Rev Drug Discov* **8**: 854–864.
51. Ramharter M *et al.* (2002) In vitro activity of tafenoquine alone and in combination with artemisinin against *Plasmodium falciparum*. *Am J Trop Med Hyg* **67:** 39–43.
52. Cooper RD *et al.* (1994) The efficacy of WR238605 against the blood stages of a chloroquine resistant strain of *Plasmodium vivax*. *Trans R Soc Trop Med Hyg* **88**: 691–692.
53. Ponsa N *et al.* (2003) Transmission-blocking activity of tafenoquine (WR-238605) and artelinic acid against naturally circulating strains of *Plasmodium vivax* in Thailand. *Am J Trop Med Hyg* **69**: 542–547.
54. Peters W *et al.* (1993) The chemotherapy of rodent malaria. LI. Studies on a new 8-aminoquinoline, WR 238,605. *Ann Trop Med Parasitol* **87**: 547–552.
55. Crockett M and Kain KC (2007) Tafenoquine: a promising new antimalarial agent. *Expert Opin Investig Drugs* **16**: 705–715.
56. Shanks GD *et al.* (2001) A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against *Plasmodium falciparum* malaria. *Clin Infect Dis* **33**: 1968–1974.
57. Hale BR *et al.* (2003) A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against *Plasmodium falciparum*. *Clin Infec. Dis* **36**: 541–549.
58. Lell B *et al.* (2000) Malaria chemoprophylaxis with tafenoquine: a randomised study. *Lancet* **355**: 2041–2045.
59. Walsh DS *et al.* (2004) Efficacy of monthly tafenoquine for prophylaxis of *Plasmodium vivax* and multidrug-resistant *P. falciparum* malaria. *J Infect Dis* **190**: 1456–1463.
60. Elmes NJ *et al.* (2008) The efficacy and tolerability of three different regimens of tafenoquine versus primaquine for post-exposure prophylaxis of *Plasmodium vivax* malaria in the Southwest Pacific. *Trans R Soc Trop Med Hyg* **102**: 1095–1101.
61. Walsh DS *et al.* (1999) Randomized dose-ranging study of the safety and efficacy of WR 238605 (Tafenoquine) in the prevention of relapse of *Plasmodium vivax* malaria in Thailand. *J Infect Dis* **180**: 1282–1287.
62. Walsh DS *et al.* (2004) Randomized trial of 3-dose regimens of tafenoquine (WR238605) versus low-dose primaquine for preventing *Plasmodium vivax* malaria relapse. *Clin Infect Dis* **39**: 1095–1103.
63. Kitchener S *et al.* (2007) Tafenoquine for the treatment of recurrent *Plasmodium vivax* malaria. *Am J Trop Med Hyg* **76**: 494–496.
64. Brueckner RP *et al.* (1998) First-time-in-humans safety and pharmacokinetics of WR 238605, a new antimalarial. *Am J Trop Med Hyg* **58**: 645–649.
65. Nasveld PE *et al.* (2010) Randomized, double-blind study of the safety, tolerability and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in non-immune subjects. *Antimicrob Agents Chemother* **54**, 792–798.
66. Dutta GP *et al.* (1989) Radical curative activity of a new 8-aminoquinoline derivative (CDRI 80/53) against *Plasmodium cynomolgi* B in monkeys. *Am J Trop Med Hyg* **41**: 635–637.
67. Gogtay NJ *et al.* (2004) Preliminary report of the evaluation of the gametocytocidal action of bulaquine, in adult patients with acute, *Plasmodium falciparum* malaria. *Ann Trop Med Parasitol* **98**: 525–528.
68. Valecha N *et al.* (2001) Comparative antirelapse efficacy of CDRI compound 80/53 (Bulaquine) vs primaquine in double blind clinical trial. *Curr Sci* **80**: 561–563.
69. Krudsood S *et al.* (2006) Safety and tolerability of elubaquine (bulaquine, CDRI 80/53) for treatment of *Plasmodium vivax* malaria in Thailand. *Korean J Parasitol* **44**: 221–228.
70. Singh B *et al.* (2004) A large focus of naturally acquired *Plasmodium knowlesi* infections in human beings. *Lancet* **363**: 1007–1024.
71. Cox-Singh J *et al.* (2008) *Plasmodium knowlesi* malaria in humans is widely distributed and potentially life-threatening. *Clinical Infectious Diseases* **46**: 165–171.
72. Daneshvar C *et al.* (2009) Clinical and laboratory features of *Plasmodium knowlesi* infection. *Clinical Infectious Diseases* **49**: 852–860.

73. Tang T *et al.* (2010) First case of detection of *Plasmodium knowlesi* in Spain by real time PCR in a traveller from Southeast Asia. *Malar J* **9**: 219–224.
74. Berry A *et al.* (2011) Imported *Plasmodium knowlesi* malaria in a French tourist returning from Thailand. *Am J Trop Med Hyg* **84**(4): 535–538.
75. William T *et al.* (2011) Severe *Plasmodium knowlesi* malaria in a tertiary care hospital, Sabah, Malaysian Borneo. *Emerg Infect Dis* **17**: 1248–1255.

THE STRATEGY OF STANDBY EMERGENCY SELF-TREATMENT

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Standby emergency treatment (SBET) is described as the self-administration of antimalarial drugs when malaria is suspected and prompt medical attention is unavailable within 24 hours of the onset of symptoms. It is indicated only in emergency situations [1] as a life-saving measure. This option is for clearly defined situations and is not intended to replace chemoprophylaxis or to detract from the importance of medical consultation when suspected malaria occurs. Some European countries recommend SBET as a stand-alone strategy for travellers to areas with low levels of *Plasmodium falciparum* transmission, but most authorities recommend the carriage of malaria SBET as an adjunct to chemoprophylaxis in case of break-through malaria [2, 3].

The goal of prophylaxis is to prevent symptomatic malarial infection, a practice, however, that carries a risk of adverse events. Depending on study design and definitions, up to 75% of users of any chemoprophylaxis will report perceived adverse events [4]. Most of these events are mild, but serious adverse events (approximately 1/10,000 users of chemoprophylaxis) [5] have been reported. These figures show that a risk-benefit analysis (adverse events versus avoided infections) is necessary for travellers minimally exposed to malaria infection. For the low-risk, malaria-endemic areas of Asia and South America, the risk of severe toxicity from chemoprophylactic drugs can actually outweigh the benefit of avoided infection, and here the SBET strategy offers an alternative option. Furthermore, it is recognised that no antimalarial prophylactic regimen gives complete protection, and this is especially true in areas of high transmission of resistant *P. falciparum*. Additional protection against breakthrough malaria can be afforded by the availability of a 'standby' emergency therapy. Thus, SBET has a place both for use alone and/or in combination with a chemoprophylactic regimen.

The rationale for national authorities who recommend SBET as a stand-alone strategy is based on a risk-benefit analysis considering malaria cases and avoided deaths versus serious adverse events. Older data estimated that the risk of acquiring malaria varied from a high of 8% per month in the Solomon Islands, to 2.4% in West Africa, to a markedly lower incidence in South and Central America (0.05% and 0.01%, respectively) [5]. Newer data from Sweden show that 302 per 100,000 visitors to West Africa will acquire malaria compared with 7.2 per 100,000 visitors to South America and 2 per 100, 000 visitors to Thailand [6]. More recently, a study [7] on the risk of malartia in travellers to India showed a marked decline in malaria imported from India and a very low proportion of *P. falciparum* malaria. This has prompted the Central European countries – Germany, Switzerland and Austria – to recommend SBET rather than continuous chemoprophylaxis for the Indian subcontinent. The risk of travellers acquiring malaria in Southeast Asia is considered very low and for most destinations does not warrant chemoprophylaxis [8]. Clearly malaria risk varies markedly according to the geographic area visited. Furthermore, priority chemoprophylaxis options such as atovaquone/proguanil, mefloquine and doxycycline will not prevent the occurrence of late-onset *P. vivax* infections. *P. vivax* is the predominant malaria species in many parts of Asia and South America. The malaria prevention guidelines for Switzerland, Germany and Austria sanction the use of the carriage of SBET as a stand-alone strategy for most of South America and Asia, including India [8–10].

Situations where carriage of SBET is indicated

- The traveller is visiting an area with a minimal malaria risk or a remote area far from medical attention.
- The traveller is using a suboptimal chemoprophylaxis (due to contraindications to priority antimalarials) or is a long-term traveller likely to have lapses in chemoprophylaxis adherence.
- The traveller is likely to have a changing itinerary and may occasionally visit high-risk malaria areas.
- The frequent traveller (e.g. aircrews, business travellers).

Options for SBET

Several antimalarials for emergency self-treatment can be recommended, but the trend is towards recommending new combination antimalarial treatments such as artemether/lumefantrine or atovaquone/proguanil, that have a simple dosage schedule and good tolerability (Table 10.5) [10]. A new artemisinin combination dihydroartemisinin/piperaquine has been recently licensed for EU

Table 10.5

Combination SBET Options	Adult dose
Arthemether/Lumefantrine (20 mg/120 mg) Riamet*	24 tablets over 3 days
Atovaquone/Proguanil (250 mg/100 mg) Malarone*	12 tablets over 3 days
Dihydroartemisinin/Piperaquine* (40mg/320mg)	3 tablets daily for 3 days **

*Preferred – effective, well tolerated ** >75kg 4 tablets daily for 3 days

Table 10.6

Year	Agent	Origin	Destination	Use (%)
1992	PYR / SDX / MQ	Swiss	Asia, Americas	0.5
1992/3	H / MQ / CL / PYR	German	Asia	0.3
1994	H / MQ / PYR SDX	German	Asia	1.0
2001	MQ / Riamet	Swiss	Asia, Americas	0

PYR/SDX/MQ: pyrimethamine/sulphadoxine/mefloquine as Fansimef ®
H: Halofantrine, MQ :mefloquine, CL: chloroquine

countries for the treatment of uncomplicated malaria and this is also a potential candidate as an SBET drug combination. The choice of SBET will depend on the expected profile drug resistance at the destination, the traveller's medical history, the prophylactic agent used (if applicable) and the ease of administration. In some cases, cost is also a factor.

Guidelines for the use of SBET

The traveller should be provided with simple written guidelines [10] to guide them in the use of SBT. The following sequence can be suggested.

1 The traveller is unwell with fever (>37.5°C) and/or other symptoms such as malaise, headache, myalgia, gastrointestinal tract symptoms or shivering.
2 Medical attention is unavailable within 24 h of onset of symptoms.
3 A minimal period of at least 6 days has elapsed since entering the malaria-endemic area.
4 The traveller reduces fever (with tepid sponging and paracetamol).
5 The SBET is administered with adequate fluids.
6 The traveller seeks medical attention at the first opportunity.

Experience with the SBET approach

European guidelines (Swiss, German, Austrian) consider most of Asia and South America to be minimal risk areas and considerable experience with the SBET approach is available. Studies have shown that SBET is unlikely to be overused by travellers who visit low-risk areas and a review of the experience to date shows that less than 1% of travellers carrying SBET will actually use their medication (Table 10.6). A study on the use of SBET in travellers to low malaria risk areas showed that 10% of travellers will become ill with symptoms that are indicative of a possible malaria. Most travellers can reach medical attention within 24 h but approximately 1% of travellers will use their SBET. Of these only a fraction will actually have malaria. In the cited study only 1 in 6 SBET users actually had malaria [10]. Thus, SBET offers a safety net for travellers who will stay in low-risk areas. The issue of counterfeit medication is also important and carriage of an SBET bought prior to travel ensures reliable quality of medication in contrast to locally bought medication that is likely to be counterfeit [11].

References

1. World Health Organization (2012)Malaria. In: *International Travel and Health*. World Health Organization, Geneva.
2. Schlagenhauf P and Petersen E (2012) Standby emergency treatment of malaria in travelers: experience to date and new developments. *Expert Rev Anti Infect Ther* **10**: 537–546.
3. Chen LH *et al.* (2007) Controversies and misconceptions in malaria chemoprophylaxis for travelers. *JAMA: J Am Med Assoc* **297**: 2251–2263.
4. Schlagenhauf P *et al.* (2003) Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. *Br Med J* **327**(7423): 1078–1081.
5. Steffen R *et al.* (1993) Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting East Africa. *Lancet* **341**(8569): 1299–1303.
6. Askling HH *et al.* (2005) Malaria risk in travelers. *Emerg Infect Dis* **11**: 436–441.
7. Schmid S *et al.* (2009) Risk of the risk of malaria in travelers to India. *J Travel Med* **16**(3): 194–199.

8. Behrens RH *et al.* (2010) The incidence of malaria in travellers to South East Asia: is local malaria transmission a useful risk indicator? *Malar J* **9**: 266.
9. Schlagenhauf P (2008) Stand-by emergency treatment of malaria by travellers. In: SChlagenhauf P (ed.) *Travelers' Malaria*, 2nd edn, pp. 316–322. BC Decker, Ontario.
10. Schlagenhauf P *et al.* (1995) Behavioural aspects of travellers in their use of malaria presumptive treatment. *Bull World Health Org* **73**: 215- 221.
11. Newton PN *et al.* (2006) Counterfeit anti-infective medicines. *Lancet Infect Dis* **6**: 602–613.

Chapter 11 Emerging and re-emerging infectious diseases

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A physician is obligated to consider more than a diseased organ, more even than the whole man – he must view the man in his world.

Harvey Cushing

Emerging travel and infectious diseases

Most human history took place in small and scattered populations. Before, few people travelled far away from their birthplace. According to the World Tourism Organization (WTO), in 1950 there were only 25 million international arrivals [1] for an estimated population of 2,521 million [2]. Since then international arrivals have grown at an average annual rate of 6.5% [1] and now almost everyone travels in one way or another. Close to 1 billion tourists crossed borders in 2008, growing nearly 20 million compared with 2007 [3]. These figures, only the tip of the iceberg, do not include domestic travel.

Now, the world is interconnected as never before. The time to reach the antipodes has shrunk from a year in 1788 to 24 hours in 2000 [4]. We can reach any place in less than 24 hours, less than the incubation period for most infectious diseases. The way of living has changed, with a progressive urbanisation of society: the United Nations projected that half of the world's population would live in urban areas at the end of 2008 [5]. The population of the world is also greater than ever (as of 18 November 2009 estimated at 6.798 billion [6]). This growing tendency in population [7] and travel is expected to continue, and the WTO forecasts that international arrivals will reach nearly 1.6 billion by 2020 [8].

As new places and new ways of living appear, the range of diseases that afflict humans also changes. More people travel and they travel faster. Microbes travel with them so they have a greater chance of being seeded in different environments where there may be new hosts. Microbes could even be returning to places from where they had been eradicated previously, with or without human intervention. It has been hypothesised that intercontinental travel would homogenise the spatial distribution of microbes [9]. However, besides travel, other ecological factors associated with the growth and dispersal of populations determine and shape the epidemiology of the infections with which we live and those that arise in a given moment. The biology and ecology of the pathogen–host interaction determine the ability of pathogens to invade new populations [10]. Ecological and biological factors, in constant change, differ around the globe. The pandemic *Influenza A(H1N1)v* virus exemplifies a successful invasion and worldwide emergence of a pathogen. Not only did travellers carry it to other continents, but also there was sufficient ongoing transmission to increase the reproduction number (defined as the average number of secondary infections caused by an index case) above 1 [11]. Swine-like influenza viruses had circulated previously, in pigs in the United States and had occasionally been transmitted to humans. However, these viruses did not transmit efficiently from human to human [11].

Air transport

The method of transport influences where, how fast and what type of microbes spread. With increasing international travel by air covering great distances in short time, human-incubated pathogens or viable insect vectors can reach far-away destinations easily. This is illustrated well by the numerous cases of 'airport malaria' in Europe, North America and elsewhere, and mosquito species settling in countries where they were not reported previously [12]. Data on the architecture of the global airline transportation network and the passengers travelling through it each year can be used to assess likely vulnerable pathways for introduction of diseases to new regions [13]. This enables preparedness to be

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considered a priority in mitigating the risks of importation at the main points of entry.

Aircrafts, as closed environments, may facilitate transmission of infectious diseases, especially those that are airborne. However, most on-board aircraft infectious disease reported events have involved food- and waterborne pathogens such as *Salmonella*, *Staphylococcus*, *Norovirus* or even *Vibrio cholerae* [14]. Airborne tuberculosis, influenza, SARS (severe acute respiratory syndrome), meningococcal disease and measles are transmitted relatively frequently on board airplanes and transmit efficiently enough to allow importation and subsequent transmission at a destination [15]. Early detection of these outbreaks, the timely risk assessment and contact tracing if needed, are critical for an efficient public health response [15].

Sea transport

The role of trade and shipping in the spread of disease has been largely studied. Relevant examples are the 16th-century syphilis epidemic, which probably returned to Europe from America on Columbus's ships [16]; the exportation to America of measles and smallpox [17]; and the spread of bubonic plague, carried by flea-infested rats on board ships, from Crimea throughout the Mediterranean and Europe [18]. The latter is believed to have reached Europe as the result of a biological warfare attack [19]. Bioterrorist attacks, a possible source for emerging diseases, represent a continuous threat, as seen in 2001 in the US when anthrax spores sent through the mail resulted in 22 cases and five deaths [20]. Some ships can be a hostile environment for people to work in, due to crowding and inadequate hygienic conditions. Infectious diseases associated with these, such as tuberculosis, are more prevalent in this occupational group, which can spread pathogen strains internationally [21]. Leisure shipping is also growing: 12 million passengers went on a cruise vacation in 2007, a 6% increase since 2006. Cruise ships, an ideal environment for air-, contact-, food- and waterborne infections, often affect an elderly, vulnerable population. The most frequently reported diseases occurring on cruises are influenza, legionellosis and norovirus [22]. Other documented sources for spread of infections on ships are ballast water, reported to carry *V. cholerae* [14], and cargo, where vectors or reservoirs can, deliberately or not, be shipped.

Road and railway transport

In the European Union (EU) during 2007, passenger cars accounted for 72.4 % of total intra-EU transport activities; buses and coaches for 8.3 %; railways for 6.1 %; and tram and metro for 1.3% [23]. There is scarce scientific evidence of infectious disease transmission in these circumstances [24], which probably underestimates their importance. As closed settings, risk of transmission for airborne diseases is higher than in open-air premises, especially when travelling long distances exposed to infective hosts. A 35% rate of tuberculin conversion has been reported among contacts of index cases using school buses [25]. Trains have also been documented as a potential vehicle for inter-regional spread of malaria vectors and malaria parasites [26].

Migrants and other mobile populations

Migrant and other mobile populations, one of the main victims and spreaders of emergent infections, have changed the epidemiology of some diseases, resulting in an increase in their geographical distribution. Migrants may be carriers of diseases endemic in their country of origin, which may contribute to a change in the prevalence of diseases at a destination. One example is that of Chagas disease, whose prevalence may change in industrialised countries that receive a high number of immigrants from disease-endemic areas [27]. Immigrants frequently travel to their country of origin. These immigrant travellers (VFRs) are known to have a higher riskof importing diseases, as they rarely seek pre-travel advice and may become infected following close contact with the local population. In Europe, VFRs who returned from sub-Saharan Africa and Indian Ocean islands can be considered a major group at risk for importing malaria as more cases of *Plasmodium falciparum* malaria occur in this specific group than any other group of travellers [28].

Refugees are a group at high risk of and a cause of subsequent outbreaks of infectious diseases given their often precarious hygienic and nutritional conditions, coupled with overcrowding. Examples of outbreaks among this group are numerous, including cholera, dysentery, scrub typhus and tuberculosis [29].

Mass gatherings

Mass gathering events pose an increased risk for outbreaks of infectious diseases, together with a potential for rapid international spread. Both have been reported in association with sporting [30] or religious events [31]. This creates significant challenges for public health and healthcare services, especially during ongoing outbreaks at venue sites that have the potential for continued transmission in a crowded setting. An example was the measles outbreak in Austria and Switzerland concurrent with the 2008 European Football Championship (Euro 2008) [32]. Preparation for this included a risk assessment organised by the European Centre for Disease Prevention and Control (ECDC) prior to Euro 2008, which concluded the ongoing outbreaks of measles in both countries could have had the potential for spreading

internationally. This enabled the publication of recommendations on immunisation for those planning to attend. The situation was monitored by coordinated epidemic intelligence and response activities at a European level. Although low-level measles transmission occurred, no cases were reported associated with the event.

Another public health challenge involved the 2009 annual Hajj to Saudi Arabia, a highly crowded international mass gathering. This was particularly in the context of ongoing pandemic *Influenza A(H1N1)v* virus transmission. The Saudi Arabian Authorities instigated preventive measures, including a change in requirements for visa entry during the Hajj and Umra seasons. WHO issued health recommendations focusing not only on pandemic (H1N1) influenza, but also regarding yellow fever, meningococcal meningitis and poliomyelitis [33]. WHO has recently published interim planning guidelines for mass gatherings with reference to pandemic (H1N1) 2009 influenza [34].

Emerging infectious diseases and travel medicine

According to the mostly used definition which originated from the US Institute of Medicine [35], emerging diseases are: '. . . those whose incidence in humans has increased within the past two decades or threatens to increase in the near future'. This definition causes problems when unavailable epidemiological data do not allow for the comparison of incidences between diseases of the past or different surveillance systems. It provides a snapshot only of those diseases that have, to our existing knowledge, become epidemiologically important in recent times. However, we should be aware that epidemics have occurred since the time of Hippocrates, and although hygiene, antibiotics and vaccines have achieved the eradication of smallpox, Pasteur's claim that it was 'within the power of man to eradicate infection from the earth' [36] is far from becoming true even today. Infections continue to appear whenever microbes, hosts and the environmental factors that put them together adjust to changes in the others. This traditional model of infectious disease causation, the epidemic triangle, functions in a dynamic way and new human pathogens continue to be described every year [37], and emerge and re-emerge in different parts of the globe [38]. Rather than being decided geographically by a point destination in a Euclidean flat world, the possibilities of survival and emergence of travelling microbes in our changing earth are determined actively, not only by the spatial but also by the temporal qualities of motion [39] (Figure 11.1).

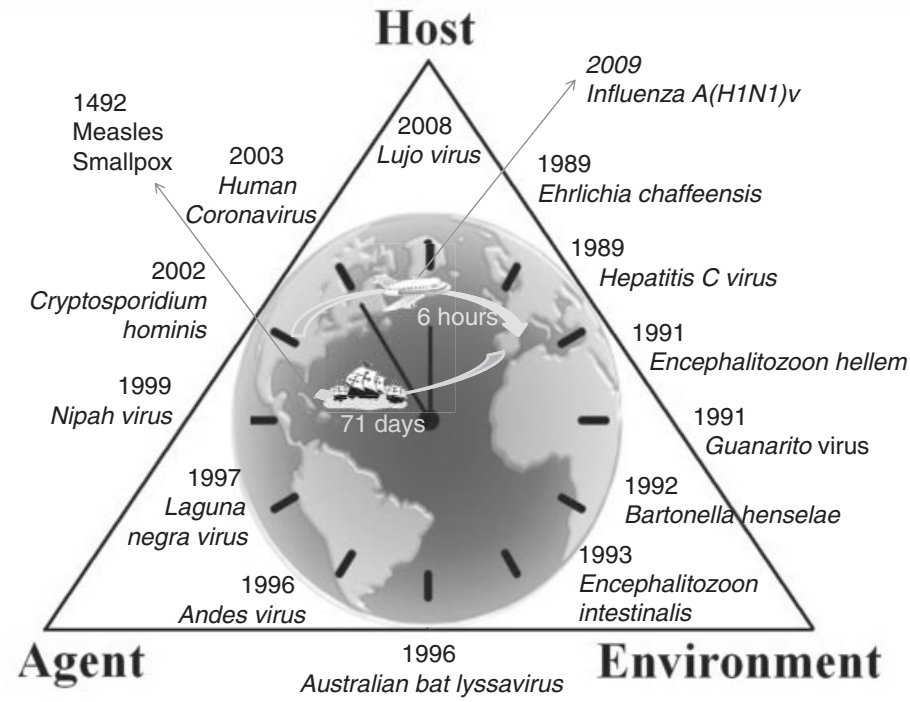

Figure 11.1 Modified epidemiological triangle model incorporating the influence of spatial and temporal qualities of motion as well as global travel in the occurrence of emerging or re-emerging infectious diseases.

Table 11.1 Emerging and re-emerging infections relevant to travel health and caused by microorganisms identified between 1989 and 2009

Year	Agent	Disease	Travel medicine association
2008 [37]	Lujo virus	Haemorrhagic fever	Associated aerosol infectivity and rapid onset of severe disease. Only described in Southern Africa [37]
2003 [84]	Human *Coronavirus*	Severe acute respiratory syndrome	Rapid international spread person to person [15]
2002 [85]	*Cryptosporidium hominis*	Cryptosporidiosis	Worldwide distribution but higher in developing countries [22]
1999 [86]	*Nipah* virus	*Nipah* virus encephalitis	Limited risk for travellers but causes severe disease and death during outbreaks (South Asia) [86]
1997 [87]	*Laguna negra* virus	Hantavirus pulmonary syndrome	Small risk for tourists engaged in outdoor activities exposed to rodents in South Cone of America [87]
1996 [89]	*Andes* virus		Uncommon but possible person-to-person transmission [88]
1996 [90]	Australian bat *lyssavirus*	Rabies-like illness	Possible exposure to black flying foxes during adventure activities in mangroves and rainforests (Australia) [90]
1993 [91]	*Encephalitozoon intestinalis*	Microsporidiosis	Causal agent of traveller's diarrhoea, especially in the immunocompromised [92]
1992 [93]	*Bartonella henselae*	Cat-scratch disease	Occurs worldwide wherever cats are found [22]
1991 [94]	*Guanarito* virus	Venezuelan haemorrhagic fever	Small risk for tourists engaged in outdoor activities exposed to rodents in areas of Venezuela [22]
1991 [95]	*Encephalitozoon hellem*	Microsporidiosis	Causes ocular microsporidiosis. Worldwide distribution
1989 [96]	*Hepatitis C* virus	Hepatitis	Approximately 3% of the world's population infected. Travellers can be exposed through direct contact with blood or contaminated equipment [22]
1989 [47]	*Ehrlichia chaffeensis*	Human monocytic ehrlichiosis	Travellers can be infected by tick bites when outdoors next to deer, dogs, ruminants and rodents [22]

The present global flora is a mixed picture drawn by major determinants such as the following.

- The immunological status of hosts: increased susceptibility due to induced immunosuppression, or on the other hand, immunisation, which limits the spread of some microbial species offering others their previous niche.
- An increase in the probabilities of hosts meeting agents through new global scenarios: deforestation (leading to increased human contact with wilderness habitats and new infectious agents), migration or travel of hosts and also of vectors and reservoirs, urbanisation, mass gatherings, changes in human behaviour (e.g. risky sexual behaviour, intravenous use of drugs, adventure travel).
- Globalisation of food and trade, which enables globalisation of pathogens.
- The natural evolution of microbes, which adapt rapidly to these new scenarios fully exploiting the niches offered. In addition, the parallel growth of livestock and human populations means more chances of mutations and variety of hosts, leading to greater microbial and disease diversity.

Comprehensive inventories of emerging and re-emerging diseases have been published elsewhere [40]. Taking this into account and limiting our field to those diseases in which travellers can play a main role or that can be important for travel medicine practitioners, we should focus on the following.

- New infections or known diseases caused by newly identified pathogens (Table 11.1).
- Existing infections with increasing public health importance owing to their geographical spread, higher incidence or virulence, or resistance to therapy (Table 11.2). The result of one or more of the following:
  - modified agents (due to spontaneous mutations, selective pressure or genetically modified *in vitro*)
  - new hosts: infections introduced in new populations (i.e. immunologically naïve) or in new species that can act as vectors or reservoirs and alter the dynamics of the disease
  - novel ecological conditions (*in situ* or after geographical relocation of pathogen or host).

Table 11.2 Emerging and re-emerging infections caused by known pathogens but with increasing travel health importance in recent years

Agent	Disease	(Re-) emergence	Travel medicine association
Influenza A(H1N1)v virus	Influenza	New triple reassortant influenza virus that emerged in April 2009 [97] with efficient human-to-human transmission [11]	Airline travel significantly contributed to the rapid spread of the virus [98] Despite initial attempts to contain spread limiting travel [99], the virus spread worldwide [100]. Travellers should observe preventive hygienic measures [101] and vaccination when indicated and available [102]
Avian Influenza A(H5N1) virus		Sporadic human cases reported since 2003 [103]. To date no efficient human-to-human transmission reported	Human infection rare but potentially severe. Travellers to countries with known outbreaks should observe adequate preventive measures [104]
Dengue virus	Dengue fever	Spread within the past 60 years to become endemic throughout all the tropics. Outbreaks extending to new countries in recent years and new serotypes circulating in already endemic countries [78]	Now considered one of the major causes of fever in ill returned travellers [28]. Surveillance in travellers should be enhanced as they can introduce it in new locations. Given also the spread of the arthropod vectors [105], this can lead to establishment in new regions [106]
Chikungunya virus	Chikungunya fever	Since 2004, progressive higher incidence and spread to new locations such as the first recorded outbreak in 2007 in Italy [107]	Surveillance in travellers should be enhanced as they can introduce it in new locations. Given also the spread of the arthropod vectors [105], this can lead to establishment in new regions [108]
West Nile virus	West Nile fever	Spreading rapidly in animals with sporadic human cases in North America [109] and different parts of Europe [110]	Despite low risk for travellers [111], physicians should have up-to-date knowledge of areas of activity as returned travellers may be affected
Yellow fever virus	Yellow fever	Epidemics increasing since the 1980s [112]	Travellers at risk in endemic areas [112]. Viraemic travellers can transmit it to countries where vectors are present [101]
Ebola virus	Ebola haemorrhagic fever	New hosts identified and evidence of species barrier crossing when an outbreak of Ebola Reston affected pigs and their handlers [113, 114]	High mortality. Low risk for travellers, but higher if exposed to fruit bats (e.g. adventure travel) [22]. May generate secondary cases, especially in hospital care settings if not promptly diagnosed in relation with breach of universal precautions [78]. Ebola Reston transmits to humans from alive sick pigs but probably low risk of developing severe disease in healthy individuals [114]
Marburg virus	Marburg haemorrhagic fever	Recent cases identified in travellers to caves harbouring bats [22]	High mortality. Low risk for travellers, but higher for visitors to bat caves in areas where outbreaks occur [22]. May generate secondary cases, especially in hospital care settings if not promptly diagnosed in relation to breach of universal precautions [78]
Lassa virus	Lassa fever	Some evidence of extension of endemicity with recent imported 'sentinel' cases to Europe from countries bordering endemic areas [115]	High mortality. Low risk for travellers, but higher for visitors to areas where outbreaks occur [22]. Physicians should be aware these areas can be larger than expected [115]. May generate secondary cases, especially in hospital care settings if not promptly diagnosed in relation to breach of universal precautions [78]
Crimean-Congo haemorrhagic fever virus	Crimean-Congo haemorrhagic fever	Increasing incidence in some countries of south-eastern Europe [116]	Low risk for travellers [22]. Cannot result in extended transmission where arthropod vector not present, but may generate secondary cases, especially in healthcare settings if not promptly diagnosed [78]

Table 11.2 (*Continued*)

Agent	Disease	(Re-) emergence	Travel medicine association
Rift Valley Fever virus	Rift Valley fever	Previously restricted to Africa, in 2000, cases were confirmed in Saudi Arabia and Yemen [117]	Low risk for travellers but they should be aware of ongoing outbreaks to avoid high-risk activities such as animal slaughtering [118]
Rabies virus and rabies-related lyssaviruses	Rabies	Bat rabies increasingly reported in the Americas [119] and Europe with sporadic human cases [120]	Treatment of international travellers after bat bites recommended [120]
Human immunodeficiency virus	Acquired immunodeficiency syndrome	Emerging in Eastern Europe and Asia [121]. Increases vulnerability to other emerging and re-emerging pathogens	High prevalence of HIV in migrant populations from prevalent countries [121]. In some European countries, a major proportion of heterosexuals with newly acquired HIV infection have acquired it while abroad [122].
Norovirus	Gastroenteritis	Increased reporting but also increased detection through new diagnostic methods [123]. Emergence of new strains with increased transmissibility [124]	High number of outbreaks associated with cruise ships in recent years which led to increased reporting of the same strains at origin of those exposed on the ships [125]. Also reported in an aircraft [126]
Hepatitis A virus	Hepatitis A	Re-emergent in some countries (e.g. Latvia [127]) and new risk groups (e.g. men who have sex with men [128])	Travellers, migrants (including international adoptees [129]) and Roma populations have the potential to spread the disease and originate distant outbreaks in low coverage vaccinated populations [130]. Cases also reported in association with cruise ships in endemic countries [131]
Hepatitis E virus	Hepatitis E	Identified in 1988 [132]. Emerging in industrialised countries where reported sporadic autochthonous cases are increasing [133, 134]	Although more frequent in travellers returning from endemic areas, this diagnosis should be considered in patients with acute hepatitis, regardless of travel history [134]. An outbreak also reported on a cruise ship [135]
Morbillivirus	Measles	Re-emerging in some industrialised countries, remarkably in Europe since 2007, associated with pockets of low vaccine coverage populations [136]	Travellers at risk if not fully immunised and visiting areas with low vaccine coverage [112]. Also at risk of leading to outbreaks if travelling ill to such areas or if contact with non-immunised groups [137]. Transmission reported in airports [138] and long-haul commercial aircrafts [15]
Rubulavirus	Mumps	Outbreaks reported in some industrialised countries in young adults, arising from transmission in so-called 'third-level colleges' [139]	Travellers at risk if not fully immunised and visiting areas with low vaccine coverage. Also at risk of leading to outbreaks if travelling ill to such areas or if contact with non-immunised groups [140]. Only one measles, mumps and rubella vaccine (MMR) dose may not protect [141]
Poliovirus	Acute flaccid paralysis	Wild poliovirus continues to spread from endemic countries to previously polio-free countries [142]	Travellers should be correctly immunised as they could potentially re-introduce the virus where pockets of inadequate vaccination coverage may exist [22]
Neisseria meningitidis	Meningoccal disease	Changes in predominant serogroups responsible for disease in some endemic countries [143]. Increasing outbreaks associated with serogroup W135 [144]	Hajj pilgrims have started multinational outbreaks and have triggered epidemics carrying epidemic strains to sub-Saharan Africa [31]. Proof of vaccination now needed, but cases can happen in vaccinated individuals [31]. These seeding events have also risk to happen in travelers to other endemic areas. Evidence of transmission in long-haul commercial aircraft [15]

(*Continued*)

Table 11.2 (*Continued*)

Agent	Disease	(Re-) emergence	Travel medicine association
Vibrio cholerae	Cholera	Significant re-emergence since 2005, in parallel with the increase in size of populations living in unsanitary conditions [145]. Explosive outbreaks in crowded refugee camps [146]	Travellers spread epidemics if moving within unsanitary locations [146]. Reported outbreaks in tourists linked to contaminated food on aircrafts and cruise ships [29]
Shigella spp.	Shigellosis	Emergence of multidrug-resistant *Shigella dysenteriae* with added resistance to quinolones in developing countries [147]	Travellers from developed to developing countries with poor sanitary conditions at an increased risk [22]
Burkholderia pseudomallei	Melioidosis	Sporadic cases increasingly reported in travellers from tropical non-endemic recognised countries [22, 148, 149]. Re-emerges in association with adverse climatic events [150]	Physicians should consider this diagnosis as a cause of severe pneumonia, even if the patient has not travelled to highly endemic areas [149]. Laboratories in non-endemic countries should be aware automated methods can misdiagnose isolates [151]
Legionella pneumohila	Legionnaires' disease or Pontiac fever	Increasing tendency in the total number and in the cases of travel-associated Legionnaires' disease from 1986 to 2006, along with improved surveillance and travel trends [152]	Affects travelers exposed to aerosolised warm water worldwide [22]. Outbreaks reported on cruise ships [22]
Mycobacterium tuberculosis	Tuberculosis (TB)	Number of global cases still increasing as a result of population growth [153]. In 2008 WHO reported multidrug-resistant tuberculosis (MDR-TB) at the highest rates ever [154]	The incidence of TB, MDR-TB and extensively drug-resistant (XDR-TB) is associated with TB re-emergence among vulnerable populations, including migrants from highly prevalent countries [155] Long-term travellers to highly endemic areas acquire the average risk for the local population [156] Evidence of transmission risk of TB and MDR-TB on long-haul commercial aircraft [15]
Leptospira spp.	Leptospirosis	Emerging epidemics in urban settings of developing countries where it has spread from its habitual rural base [157]. Associated with flooding after hurricanes [22]	Increasingly reported in travellers and residents in tropical countries [158] Reported in travellers to countries experiencing epidemics after flooding [22]
Tick-borne encephalitis virus	Tick-borne-encephalitis (TBE)	The number of cases has increased in all endemic regions in the past 30 years and new foci have been discovered [159]	Those giving travel advice should keep knowledge about the spread of risk areas up to date
Borrelia burgdorferi	Lyme disease	Spread since first identified in 1976. At present the most commonly reported arthropod-borne illness in the US and Europe and also found in Asia [160]	Those giving travel advice should keep knowledge about the spread of risk areas up to date
Rickettsiae	Rickettsioses	New rickettsial species been discovered due to the increasing use of modern molecular biological techniques. Some pathogenic for humans [161]	Increasingly imported by travellers, especially African tick-bite fever [28] [73], but cannot lead to subsequent outbreaks if vector not present

Table 11.2 (*Continued*)

Agent	Disease	(Re-) emergence	Travel medicine association
Leishmania protozoa	Leismaniasis	Since the end of the 1990s it has re-emerged related to environmental changes in various locations and spread from rural areas to peri-urban areas [162]	Those giving travel advice should keep knowledge about the spread of risk areas up to date Reported more frequently in long-term travellers than in short-term travellers [64]
Plasmodium falciparum, vivax, ovale and *malariae*	Malaria	Global rise in incidence and increase of the rate of increase since 1979 together with a rise in the population at high to moderate risk of the disease. Reappearance in urban areas and countries where previously eradicated [163] Areas with anophelism situation without malaria disease remain at constant risk for re-emergence as illustrated by the first autochthonous case in Corsica since 1972 reported in 2006 [164] Since the first cases of *P. falciparum* resistance to chloroquine appeared in Thailand in 1957, areas of resistance have extended, affecting all available drugs [165]	The frequency of imported malaria has also increased in industrialised countries, representing the most common diagnosis in ill returned patients who have a systemic febrile illness, even more in immigrant travellers visiting family and relatives (VRFs) [28] Those giving travel advice should keep knowledge about the spread of risk areas and patterns of resistance up to date [22, 101]
Plasmodium knowlesi		Found in nature in macaques and recently acknowledged as a potentially life-threatening human pathogen extending from Malaysian Borneo to Peninsular Malaysia [166]	Risk for travellers to endemic areas [167]
Schistosoma spp.	Schistosomiasis	The development of new agricultural and irrigation resources, as well as the movement of infected human populations (e.g. refugees) in Africa, the eastern Mediterranean and Asia, has spread the infection to new endemic areas [168]	Chronic schistosomiasis is highly prevalent in expatriates from endemic areas [168] Adventure tourism and other increasingly popular activities with exposure to water in endemic areas, such as African river trips, put travellers at risk [22]
Cyclospora cayetanensis	Cyclosporiasis	Since its emergence as human pathogen in the late 1970s, increasingly been described as a cause of gastrointestinal disease in children from tropical countries, travellers and the immunocompromised [169]	Cause of traveller's diarrhoea in travellers to tropical and subtropical countries. It has also caused outbreaks in industrialised countries in relation to importation of contaminated food [22]

Emerging pathogens

Viruses

Taxonomically, viruses are the most frequent identified pathogen responsible for emerging infections over the past 20 years [10]. Environmental pressure such as antiviral interventions, a transport to or development of a different ecosystem (i.e. without their usual hosts, vectors or reservoirs) or other limiting factors lead some viral populations or even species to become extinct [41]. Other viral populations adapt and re-emerge in new populations or places through different mechanisms such as recombination and reassortment [42], so selecting those genomes fit enough to generate viable quasispecies [43]. Moreover, experiments with RNA viruses have shown that they exhibit memory genomes resulting from historical selection or bottleneck events that influence the future composition of viral populations [43]. These memory genomes, when a viral population replicates in the same environment in which memory is generated, enable the dominant genomes and the memory genomes to become 'fit' enough to allow the re-emergence of a viral population [44]. Possible alterations in the environment influencing this process occur continuously, largely affected by human intervention (deforestation, urbanisation, intense agriculture and livestock production, etc.). Viruses can also travel with hosts to a different environment, enabling new adaptive possibilities to establish viral quasispecies.

In conclusion, the emergence and re-emergence of viruses is largely unpredictable because of the stochastic nature of mutation and recombination events, as well as the complexity and variety of possible environmental factors [45]. Nevertheless, retrospective pictures of the pathways of virus dispersal, significantly along migrant and trade routes, including the geographical distribution of viral lineages provided by new molecular epidemiology tools such as phylogeographies, highlight the role travellers have in spreading viral infections [46].

Bacteria

Bacteria also rapidly adapt to new conditions offered to them. New species have flourished (e.g. *Ehrlichia chaffeensis* [47]), others have become predominant (e.g. *Chlamydia trachomatis* over *Neisseria gonorrhoeae* in developed countries [48]), and existing ones have grown in virulence (eg. *Mycoplasmae* [49]) or developed new features such as antibiotic resistance (e.g. multi-drug-resistant tuberculosis [MDRTB] and extensively-drug-resistant [XDR-TB], methicillin-resistant *Staphylococcus aureus* [MRSA]).

Changes in healthcare and advances in technology have created new ecologic niches for bacteria, giving rise to new patterns of disease such as ventilator-associated pneumonia or legionellosis. *Legionella pneumophila*, first reported in 1976 [50], infects humans by aerosol inhalation or by drinking and subsequent aspiration of water. This route of infection has materialised in modern-day appliances such as 'hot tubs' or 'spa pools', hospital or hotel showers, and wet cooling towers [51].

The emergence of the acquired immunodeficiency syndrome (AIDS) and the use of new immunosuppressive treatments have increased the number of immunosuppressed patients, allowing bacteria otherwise less pathogenic to cause disease.

One of the main changes in bacterial pathogens since the use of antibacterial agents started has been the emergence of antibiotic resistance. Antimicrobial therapy brought about a rapid decline of mortality in the 1940s [52]. Since then ecologic studies based on routine surveillance data indicate a continuous rise in antimicrobial resistance associated with increased use of antimicrobials [53]. MRSA, an emerging infection due to antibiotic pressure, has become pandemic. Furthermore, although originally a nosocomial problem, emerging community-acquired MRSA has also become a worldwide problem [54]. Like many other emerging infections, it crosses the species barrier, affecting more often those in contact with pigs and cattle. Community-acquired MRSA, whose primary host seems to be pigs, can cause serious infection in humans [55].

Fungi

Invasive mycoses have emerged in the niche created by the increasing number of immunocompromised patients, the widespread use of potent antimicrobial agents, and an improvement in diagnostic and reporting procedures. These include non-albicans *Candida* species, azole-resistant *C. albicans*, *Trichosporon* and *Fusarium* species, *Zygomycetes*, *Histoplasma capsulatum*, *Penicillium marneffei* and *Coccidioides immitis* [56]. Less important epidemiologically for the travel medicine practitioner, these infections can lead to a high morbidity and mortality in the immunocompromised. *H. capsulatum and C. immitis* both can affect not only immunocompromised, but also immunocompetent individuals who travel to endemic areas and engage in risk-prone procedures [22].

P. marneffei, a high-mortality AIDS-related illness described in HIV-infected travellers to endemic areas in Southeast Asia, causes penicillosis [57]. It has also been reported in an African AIDS patient [58].

Although most fungal infections are *sapronoses*, i.e. acquired from a source in the wider environment and not

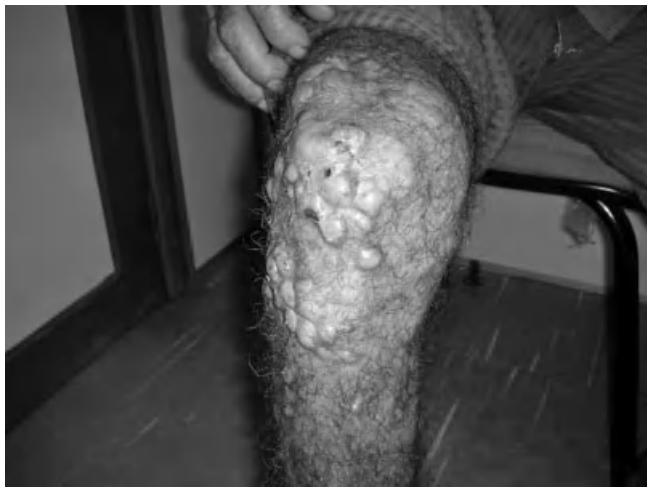

Figure 11.2 Lobomycosis. (Reproduced with permission from http://www.vacunasyviajes.es)

from another 'infection', some have animal reservoirs [10]. *P. marneffei* infects bamboo rats [57], but the most intriguing case is lobomycosis. Lobo's disease caused by *Lacazia loboi,* a never-cultured yeast-like organism, infects dolphins and humans (Figure 11.2). Although not reported to transmit human to human, one case of dolphin-to-human transmission has been documented [59]. The disease is rarely diagnosed in travellers to endemic rural regions in South America and Central America [60]. Reports of spread further north suggest an emergence of the disease that could potentially be a risk of infection in humans: in 2008 an epidemic among dolphins in the Indian River Lagoon, Florida [61], and in 2006, tqo infected stranded cetaceans off the coast of North Carolina [62].

Parasites

Parasitic diseases caused by helminths and protozoa remain one of the major causes of morbidity and mortality in tropical countries [63]. Immigrants or travellers may return from endemic areas having been infected with a parasitic disease. Relevant parasitic diseases such as malaria, leishmaniasis, filariasis, gastrointestinal parasites and schistosomiasis are reported significantly more often in long-term than short-term travellers [64].With increasing travel some are becoming emerging imported diseases. An example is gnathostomiasis, a food-borne zoonosis caused by *Gnathostoma spp.* It used to be confined to Southeast Asia and Central and South America [65], but has recently been reported in tourists returning from southern Africa [66].

As with bacteria, an emerging problem is the growing proportion of resistant parasites due to the widespread use of antiparasitic drugs. In terms of malaria, the spread of resistance limits the therapeutic choice, but it also drives virulence. Resistance to chloroquine slows the progression of replication stages and enhances transmission to mosquitoes. Less virulent plasmodia transmit easier and spread further [67].

Emerging zoonoses

In a study of 335 emerging infectious disease 'events' from 1940 to 2004, most of them were zoonoses (60.3%), mainly (71.8%) originating in wildlife (for example, severe acute respiratory virus, Ebola virus) [68]. In this study, human population density significantly predicted ($P<0.001$) emerging infectious diseases. Infectious diseases do often emerge where wildlife and crowding overlap. Many zoonotic infections include external stages in their disease cycles, which are subject to environmental conditions. Changes in these can lead to emergence or disappearance of diseases. Zoonoses' hosts are also often restricted to certain environmental conditions. This makes them prevalent in species abundant in inhabited tropics [69]. Travellers to these destinations can be at a higher risk of acquiring emerging diseases and subsequently transmitting them. This risk is higher now than ever given the trends in travel that show a growing shift in international tourist arrivals to tropical and undeveloped countries in Africa, Asia, the Pacific and Middle East [3]. The most relevant example is the human immunodeficiency virus (HIV), a descendant of a hybrid simian immunodeficiency virus capable of infecting other chimps and humans prevalent in West Africa [70]. Travel along the truck routes [71] and international travel spread the virus worldwide [72].

The constant increase in numbers of leisure travellers [3] and the changes in their behaviour towards more 'adventurous' travel can put travellers in direct contact with wildlife (e.g. primates, bats), exposing them to zoonotic diseases from which they may become carriers. Recreational activities in non-developed rural areas also heighten the risk from arthropod bites, as seen with the rise in reports of imported African tick bite fever among travellers returning from southern Africa [28, 73].

Animal reservoirs can also be domestic, and this enhances the possibility of crossing the animal–human species barrier and also of emerging infections becoming global through international trade. *Influenza A(H1N1)v* exemplifies how a domestic animal can be such a reservoir and probably mixing vessel. The virus resulted from the genetic reassortment of two different types of swine influenza with avian and human influenza elements incorporated into other swine influenza viruses (Figure 11.3). It is unclear whether the specific reassortment leading to the new virus took place in pigs or humans [11].

The geographical extension of these diseases away from their place of origin is subject to the presence of their animal

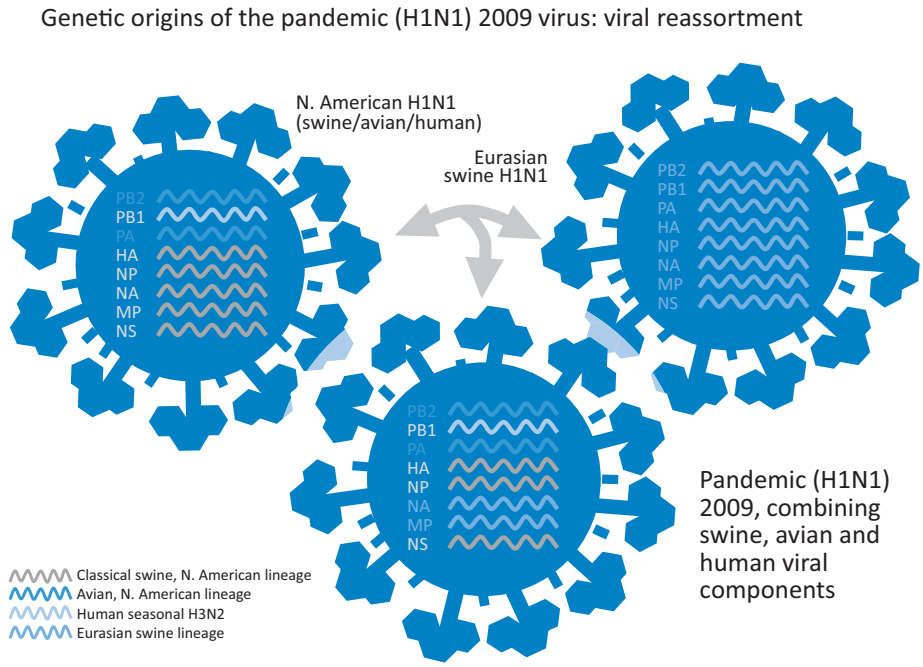

Figure 11.3 Emergence of the pandemic (H1N1) 2009 virus strain, with a mixture of swine, human and avian influenza viruses. (Reproduced from Pandemic H1N1 2009 Risk Assessment Update – Version 6 – 6 November 2009. s.l.: European Centre for Disease Prevention and Control, ECDC. 2009)

hosts, vectors or reservoirs at a destination. Mechanisms of spread include ecological disruption and climatic fluctuations such as El Niño [74], animal trade (e.g. illegal introductions to rabies-free countries of potentially infected rabid dogs from endemic areas can lead to reintroduction of rabies [75]) and introduction of competent arthropod vectors through travel and trade (e.g. *Aedes albopictus* eggs transported in used tires from northern Asia to the US in 1986 and successive spread across the continent [76]).

New molecular tools increasingly identify agents of emerging zoonoses transmitted by arthropod vectors. Between 1984 and 2005 at least 11 new rickettsial species or subspecies that cause worldwide tick-borne rickettsioses were identified. Of these, seven were initially isolated from ticks years before finding a definitive association with human disease. This has led to the description of new clinical syndromes associated with *Rickettsia* infection, such as 'TIBOLA' (for tick-borne lymphadenopathy). This syndrome is caused by *R. slovaca*, considered non-pathogenic until first reported in humans in 1997, 20 years after its discovery [77] (Figure 11.4).

Preparedness and response to emerging infectious diseases

Nobody can predict what diseases will emerge, but we do know from experience that they will continue to do so. In order to implement control measures as soon as possible, surveillance systems should be sensitive enough to detect unusual outbreaks with epidemic potential. From the natural history of the emergence of infectious disease, we can infer that the most effective preventive tool to alter spread is the application of a rapid risk assessment together with a fast and efficient response. Traditional indicator-based surveillance systems (based on the routine reporting of cases) cause delays in the detection and assessment of rare and emerging health threats. New approaches such as 'event-based surveillance', which gathers unstructured data from sources of any nature, facilitate reporting of events immediately after detection even in populations without access to formal healthcare [78]. Many countries and organisations, including the ECDC, the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), work on the early detection of emerging diseases and report on the latest public health alerts. In our globalised world, travel and travellers play an important role as sentinels, couriers and transmitters of emerging pathogens [31]. Indeed, the travel medicine practitioner should keep up to date on global communicable disease threats to enable them to contribute to their control through travel advice, early diagnosis and treatment or prophylaxis by vaccination, anti-malarials or antivirals. Updated sources of information on outbreak surveillance can be found on many websites (Table 11.3).

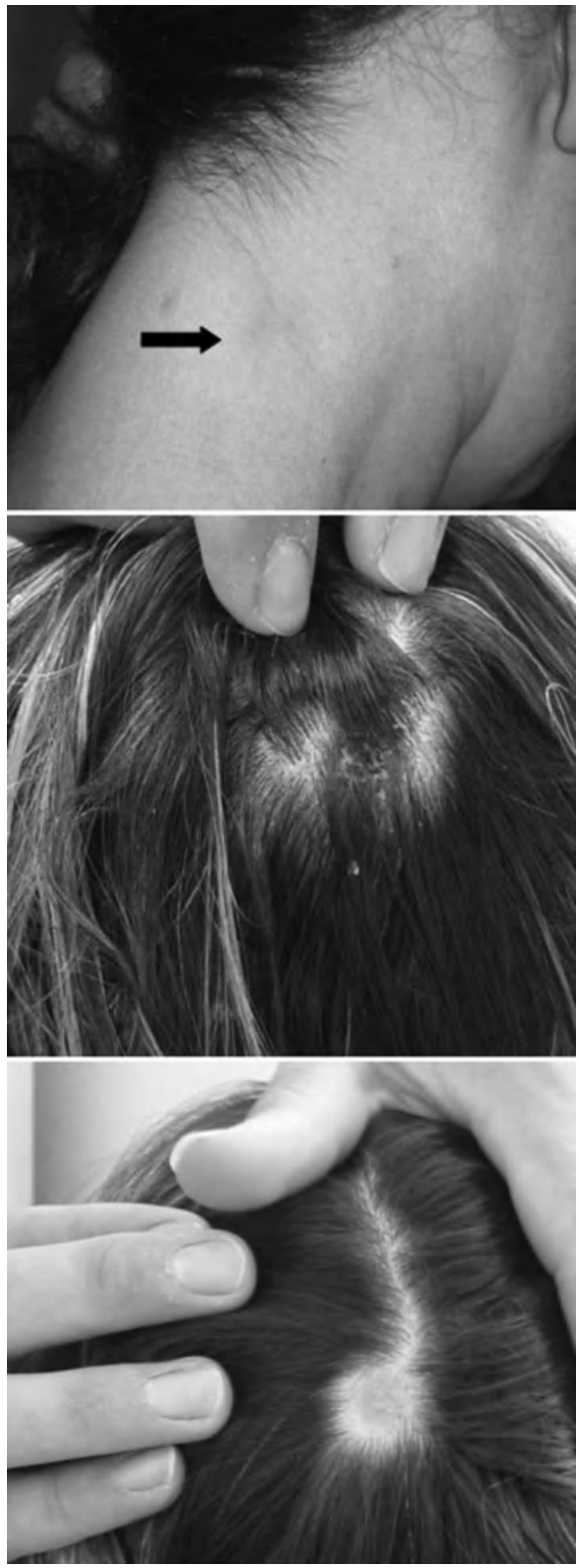

Figure 11.4 Typical signs of TIBOLA (tick-borne lymphadenopathy)/DEBONEL (Dermacentor-borne necrosis erythema and lymphadenophy). Infections were caused by *Rickettsia slovaca*, resulting in cervical lymphadenopathy (left panel, arrow), inoculation on the scalp (middle panel), and residual alopecia (right panel). (Reproduced with permission from Parola P, Rovery C, Rolain JM, Brouqui P, Davoust B, Raoult D (2009 *Rickettsia slovaca* and *R. raoultii* in tick-borne rickettsioses. *Emerg Infect Dis* 15(7): 1106)

Table 11.3 Sources of information on outbreak surveillance

Source	Website
WHO Global Alert and Response (GAR) Disease Outbreak News	http://www.who.int/csr/don/en/index.html
WHO Global Alert and Response (GAR) Pandemic (H1N1) 2009 Full Coverage	http://www.who.int/csr/disease/swineflu/en/index.html
WHO Global Alert and Response (GAR) Avian influenza webpage	http://www.who.int/csr/disease/avian_influenza/en/
WHO Global Outbreak Alert and Response Network (GOARN) [Restricted]	http://sharepoint.who.int/sites/GOARN/default.aspx
WHO Weekly Epidemiological Record (WER)	http://www.who.int/wer/2007/en/
WHO EURO: outbreaks	http://www.euro.who.int/surveillance/outbreaks/20021015_1
Pan American Health Organization (PAHO) Epidemiological Portal	http://new.paho.org/hq/index.php?option=com_content&task=view&id=220&Itemid=317
WHO SEARO (South East Asia) website	http://w3.whosea.org/
WHO cholera website	http://www.who.int/topics/cholera/en/
WHO Polioeradication program website	http://www.polioeradication.org/pressreleases.asp
US Centers for Disease Control and Prevention (CDC) Recent Outbreaks and Incidents	http://emergency.cdc.gov/recentincidents.asp
US CDC Health Alert Network	http://www2a.cdc.gov/HAN/ArchiveSys/
US CDC 2009 H1N1 Flu website	http://www.cdc.gov/h1n1flu/
US National Center for Infectious Diseases (NCID) Emerging Infectious Diseases (EID) Journal	http://www.cdc.gov/ncidod/eid/index.htm
US CDC Morbidity and Mortality Weekly Report (MMWR) Series	http://www.cdc.gov/mmwr/
The International Society of Travel Medicine (ISTM) Outbreak News and Updates website	http://www.istm.org/WebForms/NonIstmLinks/Outbreak_News.aspx#ecdc
Program for Monitoring Emerging Diseases from the International Society for Infectious Diseases (ProMed-mail)	www.promedmail.org
ECDC (European Centre for Disease Prevention and Control) news and press releases	http://ecdc.europa.eu/en/press/news/Pages/News.aspx
Eurosurveillance weekly	http://www.eurosurveillance.org
MediSys (Medical Information System)	http://medusa.jrc.it/medisys/homeedition/all/home.html.
Healthmap Global Disease Alert Map	http://www.healthmap.org
Biocaster Global Health Monitor (National Institute of Informatics, Japan)	http://biocaster.nii.ac.jp/
Global Public Health Intelligence Network (GPHIN), Public Health Agency of Canada [Restricted]	https://www.gphin.net
GIDEON (background epidemiological data)	www.gideononline.com
AlertNet (Reuters)	http://www.alertnet.org
The World Organisation for Animal Health (OIE) alert messages	http://www.oie.int/eng/info/en_urgences.htm
Newslab, health section (Russian health news)	http://english.newslab.ru/about/
Epiwatch (from Epinorth): news about outbreaks of communicable diseases from the Nordic and Baltic countries and the Russian Federation	http://www.epinorth.org/eway/default.aspx?pid=230&trg=MainArea_5260&MainArea_5260=5340:0:15,3019:1:0:0:::0:0
Hong Kong Avian Flu monitoring	http://www.info.gov.hk/info/flu/eng/global.htm
CIDRAP (Center for Infectious Disease Research and Policy from the University of Minnesota)	http://www.cidrap.umn.edu/index.html
French Institut de veille sanitaire (INVS) weekly bulletin	http://www.invs.sante.fr/beh/
INVS press releases	http://www.invs.sante.fr/actualite/index.htm
UK Health Protection Agency (HPA) weekly bulletin	http://www.hpa.org.uk/hpr/
UK HPA news	http://www.hpa.org.uk/hpr/news/
Food and Agriculture Organization of the United Nations (FAO) Avian Flu webpage (and periodic reports)	http://www.fao.org/ag/againfo/subjects/en/health/diseases-cards/avian_update.html
Specific link to EUVAC.NET (European surveillance network for vaccine-preventable diseases) homepage	http://www.euvac.net/graphics/euvac/index.html

WHO has recently revised and updated the International Health Regulations (IHR) which have been adapted to represent the current volume of international traffic and trade and help respond to diseases that can spread far and wide, including emerging infections [79]. The objectives of IHR, which include decreasing the risk of international transmission, the importation and re-introduction of disease, are legally binding for 194 countries across the globe. These regulations are usually incorporated into national laws and include separate regulations for ships, aircraft and other international conveyances.

The public health response to these emerging diseases should include multidisciplinary teams and partnerships among infectious diseases and travel medicine clinicians, epidemiologists, microbiologists, veterinarians and even entomologists, given the high proportion of vector-borne diseases. Dedicated disease and non-disease specific public health networks exist (e.g. EUVAC.NET, http://www.euvac.net/, and EWGLINET, http://www.ewgli.org/) and others are being created, not only by epidemiologists, but also by microbiologists (e.g. ENVID, http://www.enivd.de/) and entomologists (e.g. VBORNET [80]). As part of this response, recently created sentinel networks of travel medicine providers collect data on travel-related diseases that inform public health authorities, health professionals and the public. These initiatives include a worldwide network, Geosentinel (developed through a collaborative agreement between the International Society of Travel Medicine and the CDC) [81], and others that focus only on travellers returning to Europe: TropNet Europe [82] and Eurotravnet (funded by ECDC) [83]. In the long term, in order to be prepared for new emergent threats, research priorities should focus on identifying risk factors for exposure and spread of infectious diseases, including surveillance strategies, early warning and response, as these determine their epidemic potential. Given their importance, surveillance of emerging zoonoses in animals should also be enhanced.

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References

1. World Tourism Oganization (2006) *Tourism Market Trends, 2006 Edition – Annex*. World Tourism Organization, Madrid.
2. United Nations (2004) *The World at Six Billion*. United Nations, New York.
3. World Tourism Organization (2009) UNWTO World Tourism Barometer. October 2009. Volume 7, issue 3.
4. Cliff A and Haggett P (2004) Time, travel and infection. *Br Med Bull* **69**: 87–99.
5. The Associated Press (2008) UN says half the world's population will live in urban areas by end of 2008. *International Herald Tribune* 26 February, http://www.iht.com/articles/ap/2008/02/26/news/UN-GEN-UN-Growing-Cities.php (accessed 18 November 2009).
6. US Census Bureau (2009) World POPClock Projection, http://www.census.gov/population/popclockworld.html (accessed 18 November 2009).
7. United Nations (2005) *World Population Prospects: The 2006 Revision, Highlights*. United Nations, New York.
8. World Tourism Organization (2001) *Unwto's Tourism 2020 Vision*. World Tourism Organization, Madrid.
9. Haggett P (1994) Geographical aspects of the emergence of infectious diseases. The changing geography of disease distributions. *Geogr Ann Ser B* **72**(2): 91–104.
10. Woolhouse M and Rustom A (2008) Emergence of new infectious diseases. In: Stearns S.C. and Koella J.C. (eds) *Evolution in Health and Disease*, vol. 16, 2nd edn, pp. 216–217. Oxford University Press, Oxford.
11. European Centre for Disease Prevention and Control (ECDC) (2009) *Pandemic H1N1 2009 Risk Assessment Update Version 6, 6 November 2009*. ECDC, Stockholm.
12. Gratz NG *et al.* (2000) Why aircraft disinsection? *Bull World Health Org* **78**(8): 995–1004.
13. Toronto Hospital, The Centre for Research on Inner City Health. St. Michael's (2009) An Analysis of Canada's Vulnerability to Emerging Infectious Disease Threats via the Global Airline Transportation Network. *The Bio.Diaspora Project*. [Online], http://www.biodiaspora.com (accessed 18 Novemeber 2009).
14. Chen LH and Wilson ME (2008) The role of the traveler in emerging infections and magnitude of travel. *Med Clin North Am* **92**(6): 1409–1432, xi.
15. Schenkel K *et al.* (2009) *Risk Assessment Guidelines for Infectious Diseases Transmitted on Aircrafts*. European Centre for Disease Prevention and Control (ECDC), Robert Koch Institute, Berlin, Germany.
16. Jeanselme E (1933) Histoire de la Syphilis: Son Origine. *Son Expans* **19**: 1.
17. Hays JN (2005) *Epidemics and Pandemics: Their Impacts on Human History*. ABC-CLIO, Inc, Santa Barbara, CA, pp. 88–89.
18. Guy G *et al.* (1997) *Inventarium Sive Chirurgia Magna*. EJ Brill, Leiden.
19. Wheelis M (2002) Biological warfare at the 1346 siege of Caffa. *Emerg Infect Dis* **8**(9). [serial online], http://www.cdc.gov/ncidod/EID/vol8no9/01-0536.htm (accessed 10 November 2009).
20. Jernigan DB *et al.* (2002) Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. *Emerg Infect Dis* **8**(10). [serial online], http://wwwnc.cdc.gov/eid/article/8/10/02-0353.htm (accessed 10 November 2009).
21. Pesqueira P *et al.* (2007) High incidence of tuberculosis in deep sea fishermen. *Med Marit* **7**(1): 15–25.

22. Brunette GW *et al.* 2009. *CDC Health Information for International Travel 2010*. Mosby Ltd, Atlanta, GA.
23. Eurostat, European Communities (2009) *EU Energy and Transport in Figures.Statistical Pocketbook 2009*. Office for Official Publications of the European Communities, Luxembourg.
24. Witt MD (1999) Trains, travel, and the tubercle. *Clin Infect Dis* **28**(1): 57–58.
25. Poggensee G *et al.* (2009) *Systematic Literature Review on the Transmission of Communicable Diseases in Public Ground Conveyances*. European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE 2009), Stockholm.
26. Fox E *et al.* (1991) Plasmodium falciparum travels by train from Ethiopia to Djibouti. *Med Trop (Mars)* **51**(2): 185–189.
27. Monge-Maillo B *et al.* (2009) Imported infectious diseases in mobile populations, Spain. *Emerg Infect Dis* **15**(11): 1745–1752. [serial on the internet], http://www.cdc.gov/eid/content/15/11/1745.htm (accessed 20 November 2009).
28. Gautret P *et al.* (2009) Multicenter EuroTravNet/GeoSentinel study of travel-related infectious diseases in Europe. *Emerg Infect Dis* **15**(11). http://www.cdc.gov/EID/content/15/11/1783.htm (accessed 11 November 2009).
29. Ostroff SM and Kozarsky P (1998) Emerging infectious diseases and travel medicine. *Infect Dis Clin North Am* **12**(1): 231–241.
30. Cai W *et al.* (2009) Epidemic Intelligence Activities during the Beijing 2008 Olympic Games. October 2009. European Scientific Conference on Applied Infectious Disease Epidemiology' (ESCAIDE 2009).
31. Wilson ME (2003) The traveller and emerging infections: sentinel, courier, transmitter. *J Appl Microbiol* **94**: 1S–11S.
32. Kreidl P *et al.* (2008) 2008 European Football Championship – ECDC epidemic intelligence support. *Euro Surveill* **13**(32): 18946.
33. World Health Organization (WHO) (2009) WHO Health conditions for travellers to Saudi Arabia for the pilgrimage to Mecca (Hajj). *Wkly Epidemiol Rec* **84**: 477–480. [Online], http://www.who.int/wer/2009/wer8446.pdf (accessed 22 November 2009).
34. World Health Organization (WHO) (2009) Interim Planning Considerations for Mass Gatherings in the Context of Pandemic (H1N1) 2009 Influenza. *World Health Organization (WHO)*. [Online], http://www.who.int/csr/resources/publications/swineflu/cp002_2009-0511_planning_considerations_for_mass_gatherings.pdf (accessed 30 November 2009).
35. Committee on Emerging Microbial Threats to Health, Institute of Medicine (1992) Chapter 2. In: Shope RE, Oaks SC Jr and Lederberg J. (eds)*Emerging Infections: Microbial Threats to Health in the United States*, p. 34. National Academy Press, Washington, DC.
36. Dubos R and Dubos J (1953) *The White Plague: Tuberculosis, Man and Society*. Gollancz, London.
37. Briese T *et al.* (2009) Genetic detection and characterization of lujo virus, a new hemorrhagic fever–associated arenavirus from Southern Africa. *PLoS Pathog* **5**(5): e1000455. doi: 10.1371/journal.ppat.1000455
38. Rezza G *et al.*, CHIKV Study Group (2007) Infection with chikungunya virus in Italy: an outbreak in a temperate region. *Lancet* **370**(9602): 1840–1846.
39. Wald RM (1992) *Space, Time and Gravity: The Theory O the Big Bang and Black Holes*. Chicago Press, Chicago, IL.
40. National Institute of Allergy and Infectious Diseases (2009) *List of NIAID Emerging and Re-Emerging Infectious Diseases*. US Department of Health and Human Services, Washington, DC, http://www3.niaid.nih.gov/topics/emerging/list.htm (accessed 19 November 2009).
41. Domingo E *et al.* (2005) Quasispecies dynamics and RNA virus extinction. *Virus Res* **107**(2): 129–139.
42. Domingo E *et al.* (2008) Future prospects for the treatment of rapidly evolving viral pathogens: insights from evolutionary biology. *Expert Opin Biol Ther* **8**(10): 1455–1460.
43. Domingo E (2007) Virus evolution. In: Howley P. and Knipe D. (eds) *Fields' Virology*, pp. 389–421. Lippincott-Williams & Wilkins, Philadelphia, PA.
44. Arias A *et al.* (2004) Fitness increase of memory genomes in a viral quasispecies. *J Mol Biol* **339**: 405–412.
45. Duarte EA *et al.* (1994) RNA virus quasispecies: significance for viral disease and epidemiology. *Infect Agents Dis* **3**(4): 201–214.
46. Paraskevis D *et al.* (2009) Tracing the HIV-1 subtype B mobility in Europe: a phylogeographic approach. *Retrovirology* **6**: 49.
47. Anderson BE *et al.* (1991) *Ehrlichia chaffeensis*, a new species associated with human ehrlichiosis. *J Clin Microbiol* **29**(12): 2838–2842.
48. Catchpole MA (1996) The role of epidemiology and surveillance systems in the control of sexually transmitted diseases. *Genitourin Med* **72**(5): 321–329.
49. Rosengarten R *et al.* (2001) The changing image of mycoplasmas: from innocent bystanders to emerging and reemerging pathogens in human and animal diseases. In: Schäfer K.P. and Mühldorfer I. (eds) *Emerging Bacterial Pathogens. Contributions to Microbiology*, vol. 8, pp. 166–185. Karger, Basel.
50. McDade JE *et al.* (1977) Legionnaires' disease: isolation of a bacterium and demonstration of its role in other respiratory disease. *N Engl J Med* **297**: 1197–1203.
51. Sonder GJ *et al.* (2008) Changes in prevention and outbreak management of Legionnaires' disease in the Netherlands between two large outbreaks in 1999 and 2006. *Euro Surveill* **13**(38): 18983, http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18983 (accessed 18 November 2009).
52. Armstrong GL *et al.* (1999) Trends in infectious disease mortality in the United States during the 20th century. *JAMA: J Am Med Assoc* **281**(1): 61–66.
53. Sande-Bruinsma N *et al.* (2008) Antimicrobial drug use and resistance in Europe. *Emerg Infect Dis* **14**(11): 1722–1730. [serial on the internet], http://www.cdc.gov/EID/content/14/11/1722.htm (accessed 10 November 2009).
54. Vandenesch F *et al.* (2003) Community-acquired methicillin-resistant staphylococcus aureus carrying panton-valentine leukocidin genes: worldwide emergence. *Emerg Infect Dis* **9**(8): 978–984.
55. van Loo I *et al.* (2007) Emergence of methicillin-resistant *Staphylococcus aureus* of animal origin in humans. *Emerg Infect Dis* **13**(12). [serial on the Internet], http://www.cdc.gov/EID/content/13/12/1834.htm (accessed 20 November 2009).
56. Fleming RV (2002) Emerging and less common fungal pathogens. *Infect Dis Clin North Am* **16**(4): 915–933, vi–vii.

57. Carey J *et al.* (2005) *Penicillium marneffei* infection in an immunocompromised traveler: a case report and literature review. *J Travel Med* **12**(5): 291–294.
58. Lo Y *et al.* (2000) Disseminated *Penicillium marneffei* infection in an African AIDS patient. *Trans R Soc Trop Med Hyg* **94**(2): 187.
59. Symmers WS (1983) A possible case of Lobo's disease acquired in Europe from a bottle-nosed dolphin (*Tursiops truncatus*). *Bull Soc Pathol Exot Filiales* **76**(5 Pt 2): 777–784.
60. Al-Daraji WI (2008) Cutaneous lobomycosis: a delayed diagnosis. *Am J Dermatopathol* **30**(6): 575–577.
61. Reif JS *et al.* (2006) Lobomycosis in Atlantic bottlenose dolphins from the Indian River Lagoon, Florida. *J Am Vet Med Assoc* **228**(1): 104–108.
62. Rotstein DS *et al.* (2009) Lobomycosis in offshore bottlenose dolphins (*Tursiops truncatus*), North Carolina. *Emerg Infect Dis* **15**(4): 588–590.
63. World Health Organization (WHO) (2009) WHO > programmes and projects > Initiative for Vaccine Research (IVR) > selection of diseases in IVR portfolio. *Parasit Dis* [Online], http://www.who.int/vaccine_research/diseases/soa_parasitic/en/index.html (accessed 3 May 2012).
64. Chen LH *et al.* (2009) Illness in long-term travelers visiting GeoSentinel clinics. *Emerg Infect Dis* **15**(11): 1773–1782, http://www.cdc.gov/EID/content/15/11/1773.htm (accessed 20 November 2009).
65. Górgolas M *et al.* (2003) Cutaneous and medullar gnathostomiasis in travelers to Mexico and Thailand. *J Travel Med* **10**(6): 358–361.
66. Herman JS and Chiodini PL (2009) Gnathostomiasis, another emerging imported disease. *Clin Microbiol Rev* **22**(3): 484–492.
67. Koella JC and Turner P (2007) Evolution of parasites. In: Koella J.C. and Stearns S.C. (eds) *Evolution in Health and Disease*, vol. 17, 2nd edn, pp. 229–237. Oxford University Press, Oxford.
68. Jones KE *et al.* (2008) Global trends in emerging infectious diseases. *Nature* **451**: 990–993.
69. Guégan J-F *et al.* (2007) Global spatial patterns of infectious diseases and human evolution. In: Koella J.C. and Stearns S.C. (eds) *Evolution in Health and Disease*, vol. 2, 2nd edn, pp. 19–29. Oxford University Press, Oxford.
70. Bailes E *et al.* (2003) Hybrid origin of SIV in chimpanzees. *Science* **300**: 1713.
71. Lydie N and Robinson NJ (1998) West and central Africa. *Int Migr* **36**(4): 469–511.
72. Memish ZA and Osoba AO (2003) Sexually transmitted diseases and travel. *Int J Antimicrob Agents* **21**(2): 131–134.
73. Jensenius M *et al.* (2009) Multicenter GeoSentinel analysis of rickettsial diseases in international travelers, 1996–2008. *Emerg Infect Dis* **15**(11); 1791–1798, http://www.cdc.gov/EID/content/15/11/1791.htm (accessed 20 November 2009).
74. Barrett R *et al.* (1998) Emerging and re-emerging infectious diseases: the third epidemiologic transition. *Ann Rev Anthropol* **27**: 247–271.
75. Steffens I and Ekdahl K (2008) Rabies – a recurrent danger to European countries from dogs introduced from endemic countries. *Euro Surveill* **13**(19): 18870, http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18870 (accessed 19 November 2009).
76. Moore CG and Mitchell CJ (1997) Aedes albopictus in the United States: ten-year presence and public health implications. *Emerg Infect Dis* **3**(3): 329–334.
77. Parola P *et al.* (2005) Tick-borne rickettsioses around the world: emerging diseases challenging old concepts. *Clin Microbiol Rev* **18**(4): 719–756.
78. Bohigas PA *et al.* (2009) Epidemic intelligence and travel-related diseases: ECDC experience and further developments. *Clin Microbiol Infect* **15**(8): 734–739.
79. World Health Organization (WHO) (2005) *International Health Regulations (IHR)*. WHO, Geneva, http://www.who.int/entity/ihr/9789241596664/en/index.html (accessed 20 November 2009).
80. ECDC (European Centre for Disease Prevention and Control) (2009) Network of Medical Entomologists and Public Health Experts (VBORNET). *ECDC Portal > English > Activities > Disease Programmes*. [Online], http://ecdc.europa.eu/en/activities/diseaseprogrammes/Pages/VBORNET.aspx (accessed 2 December 2009).
81. Freedman DO *et al.* (1999) l: GeoSentinel: the global emerging infections sentinel network of the International Society of Travel Medicine. *J Travel Med* **6**(2): 94–98.
82. Ross K (2006) Tracking the spread of infectious diseases. *EMBO Rep* **7**(9): 855–858.
83. Schlagenhauf P *et al.* (2009) Invitation to become part of the European Travel Medicine Inventory. *Eurosurveillance* **14**: 19245, http://www.eurosurveillance.org/ViewArticle (accessed 19 November 2009).
84. Poon LLM (2007) SARS and other 'new' coronaviruses. In: Thiel V. (ed.) *Coronaviruses: Molecular and Cellular Biology*, p. 14. Caister Academic Press, Norfolk.
85. Morgan-Ryan UM *et al.* (2002) Cryptosporidium hominis n. sp. (Apicomplexa: Cryptosporidiidae) from Homo sapiens. *J Eukaryot Microbiol* **49**(6): 433–440.
86. World Health Organization (WHO) (2009) *Fact Sheet N°262: Nipah Virus*, World Health Organization, Geneva, http://www.who.int/mediacentre/factsheets/fs262/en/print.html (accessed 19 November 2009).
87. Johnson AM *et al.* (1997) Laguna Negra virus associated with HPS in western Paraguay and Bolivia. *Virology* **238**(1): 115–127.
88. Padula PJ *et al.* (1998) Hantavirus pulmonary syndrome outbreak in Argentina: molecular evidence for person-to-person transmission of Andes virus. *Virology* **241**(2): 323–330.
89. López N *et al.* (1996) Genetic identification of a new hantavirus causing severe pulmonary syndrome in Argentina. *Virology* **220**(1): 223–226.
90. Samaratunga H *et al.* (1998) Non-rabies Lyssavirus human encephalitis from fruit bats: Australian bat Lyssavirus (pteropid Lyssavirus) infection. *Neuropathol Appl Neurobiol* **24**(4): 331–335.
91. Curry A and Canning EU (1993) Human microsporidiosis. *J Infect* **27**(3): 229–236.
92. Raynaud L *et al.* (1998) Identification of *Encephalitozoon intestinalis* in travelers with chronic diarrhea by specific PCR amplification. *J Clin Microbiol* **36**: 37–40.
93. Regnery RL *et al.* (1992) Characterization of a novel Rochalimaea species, *R. henselae* sp. nov., isolated from blood of a febrile,

human imimmunodeficiency virus-positive patient. *J Clin Microbiol* **30**: 265–274.
94. Tesh RB *et al.* (1994) Description of Guanarito virus (Arenaviridae: Arenavirus), the etiologic agent of Venezuelan hemorrhagic fever. *Am J Trop Med Hyg* **50**: 452–459.
95. Didier ES *et al.* (1991) Isolation and characterization of a new human microsporidian, *Encephalitozoon hellem* (n. sp.), from three AIDS patients with keratoconjunctivitis. *J Infect Dis* **163**: 617–621.
96. Choo QL *et al.* (1989) Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* **244**(4902): 359–362.
97. Centers for Disease Control and Prevention (CDC) (2009) Swine influenza A (H1N1) infection in two children – Southern California, March-April 2009. *MMWR Morb Mortal Wkly Rep* **58**(15): 400–402.
98. Khan K *et al.* (2009) Spread of a novel influenza A (H1N1) virus via global airline transportation. *N Engl J Med* **361**(2): 212–214.
99. Anonymous (2009) Pre-empting a pandemic-fact or fiction? *Lancet* **373**(9675): 1578.
100. World Health Organization (WHO) (2009) Influenza A(H1N1) – Update. *Pandemic (H1N1) 2009 – update 75*. [Online] 20 November 2009, http://www.who.int/csr/don/2009_11_20a/en/index.html (accessed 20 November 2009).
101. World Health Organization (WHO) (2009) WHO International Travel and Health. *World – Influenza A (H1N1) Update for travelers*. [Online] 28 April 2009, http://www.who.int/entity/ith/updates/2009_04_28/en/index.html (accessed 20 November 2009).
102. World Health Organization (WHO) (2009) WHO Global Alert and Response (GAR). *Use of the pandemic (H1N1) 2009 vaccines*. [Online] 30 October 2009, http://www.who.int/csr/disease/swineflu/frequently_asked_questions/vaccine_preparedness/use/en/index.html (accessed 30 November 2009).
103. World Health Organization (WHO) (2009) *H5N1 Avian Influenza: Timeline of Major Events*. WHO, Geneva.
104. World Health Organization (WHO) (2005) *WHO Recommendations Relating to Travellers Coming from and Going to Countries Experiencing Outbreaks of Highly Pathogenic H5N1 Avian Influenza*. WHO, Geneva.
105. European Centre for Disease Prevention and Control (2009) Development of Aedes Albopictus Risk Maps. *ECDC*. [Online], http://ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=350 (accessed 30 November 2009).
106. Effler PV *et al.* (2005) Dengue fever, Hawaii, 2001–2002. *Emerg Infect Dis* **11**(5): 742–749.
107. Staples JE *et al.* (2009) Chikungunya fever: an epidemiological review of a re-emerging infectious disease. *Clin Infect Dis* **49**(6): 942–948.
108. ECDC (2007) Mission Report: Chikungunya in Italy. 2007, Joint ECDC/WHO Visit for a European Risk Assessment. 17–21 September. ECDC, http://ecdc.europa.eu/en/healthtopics/documents/0709_chikungunya_fever_mission_report.pdf (accessed 20 November 2009).
109. Brault AC (2009) Changing patterns of West Nile virus transmission: altered vector competence and host susceptibility. *Vet Res* **40**(2): 43.
110. ECDC (2009) ECDC. West Nile Fever – Factsheet. [Online], http://ecdc.europa.eu/en/healthtopics/Pages/West_Nile_Fever_Factsheet.aspx (accessed 20 November 2009).
111. National Travel Health Network and Centre (NaTHNaC), United Kingdom (2005) National Travel Health Network and Centre (NaTHNaC). *Travel Health Information Sheets: West Nile virus*. [Online], http://www.nathnac.org/travel/factsheets/west_nile.htm#_Risk_for_travellers (accessed 20 November 2009).
112. World Health Organization (WHO) (2009) *International Travel and Health 2009*. WHO, Geneva.
113. Barrette RW *et al.* (2009) Discovery of swine as a host for the Reston ebolavirus. *Science* **325**(5937): 204–206.
114. World Health Organization (WHO) (2009) Outbreak news. Ebola Reston in pigs and humans, Philippines. *Wkly Epidemiol Rec* **84**(7): 49–50.
115. Atkin S *et al.* (2009) The first case of Lassa fever imported from Mali to the United Kingdom, February 2009. *Eurosurveillance* **14**(10): pii=19145.
116. Papa A *et al.* (2009) Emergence of Crimean-Congo haemorrhagic fever in Greece. *Clin Microbiol Infect* **16**: 843–847.
117. Ahmed J *et al.* (2009) International network for capacity building for the control of emerging viral vector-borne zoonotic diseases: ARBO-ZOONET. *Euro Surveill* **14**(12): pii: 19160.
118. Rafiq SM *et al.* (2009) Hazards of hepatitis at the Hajj. *Travel Med Infect Dis* **7**(4): 239–246.
119. World Health Organization (WHO) (2008) Fact Sheet N°99: Rabies. *WHO*. [Online] December 2008, http://www.who.int/mediacentre/factsheets/fs099/en/ (accessed 21 Novemeber 2009).
120. Stantic-Pavlinic M (2005) Public health concerns in bat rabies across Europe. *Euro Surveill* **10**(11): 576.
121. European Centre for Disease Prevention and Control (ECDC) (2009) *Migrant Health Series: Epidemiology of HIV and AIDS in Migrant Communities and Ethnic Minorities in EU/EEA Countries*. European Centre for Disease Prevention and Control (ECDC), Stockholm, http://ecdc.europa.eu/en/publications/Publications/0907_TER_Migrant_health_HIV_Epidemiology_review.pdf (accessed 21 November 2009).
122. Steffen R *et al.* (2003) Travel epidemiology – a global perspective. *Int J Antimicrob Agents* **21**(2): 89–95.
123. Estes MK *et al.* (2006) Noroviruses everywhere: has something changed? *Curr Opin Infect Dis* **19**(5): 467–474.
124. Koopmans M (2009) *Insights into Norovirus Epidemiology through Molecular Epidemiological Studies*, Abstract Book. European Scientific Conference on Applied Infectious Diseaseases Epidemiology (ESCAIDE), Stockholm, 26–28 October, p. 10.
125. Verhoef L *et al.* (2008) Emergence of new norovirus variants on spring cruise ships and prediction of winter epidemics. *Emerg Infect Dis* **14**(2): 238–243.
126. Widdowson M-A *et al.* (2005) Probable transmission of norovirus on an airplane. *JAMA: J Am Med Assoc* **293**: 1859–1860.
127. Perevoscikovs J *et al.* (2009) Community-wide outbreak of hepatitis A in Latvia in 2008 – an update. *Euro Surveill* **14**(3): 19092.
128. Tortajada C *et al.* (2009) Outbreak of hepatitis A among men who have sex with men in Barcelona, Spain, September 2008 – March 2009. *Euro Surveill* **14**(15): 19175.

129. Fischer GE *et al.* (2008) Hepatitis A among international adoptees and their contacts. *Clin Infect Dis* **47**(6): 812–814.
130. Payne L and Coulombier D (2009) Hepatitis A in the European Union: responding to challenges related to new epidemiological patterns. *Euro Surveill* **14**(3): 19101.
131. Robesyn E *et al.* (2009) Cluster of hepatitis A cases among travellers returning from Egypt, Belgium, September through November 2008. *Euro Surveill* **14**(3): 19095.
132. Arankalle VA *et al.* (1988) Aetiological association of a virus-like particle with enterically transmitted non-A, non-B hepatitis. *Lancet* **1**(8585): 550–554.
133. Dalton HR *et al.* (2008) Hepatitis E: an emerging infection in developed countries. *Lancet Infect Dis* **8**(11): 698–709.
134. Norder H *et al.* (2009) Endemic hepatitis E in two Nordic countries. *Euro Surveill* **14**(19): 19211.
135. Said B *et al.* (2009) Hepatitis E outbreak on cruise ship. *Emerg Infect Dis* **15**(11): 1738–1744.
136. Muscat M *et al.*, EUVAC.NET Group (2009) Measles in Europe: an epidemiological assessment. *Lancet* **373**(9661): 383–389.
137. Pfaff G *et al.* (2008) Measles in south-west Germany imported from Switzerland – a preliminary outbreak description. *Euro Surveill* **13**(8): 8044.
138. Coleman KP and Markey PG (2009) Measles transmission in immunized and partially immunized air travellers. *Epidemiol Infect* **138**: 1012–1015. doi: 10.1017/S0950268809991129
139. Whyte D *et al.* (2009) Mumps epidemiology in the Mid-West of Ireland 2004–2008: increasing disease burden in the university/college setting. *Euro Surveill* **14**(16): 19182.
140. Polgreen PM. *et al.* (2009) A spatial analysis of the spread of mumps: the importance of college students and their spring-break-associated travel. *Epidemiol Infect* **9**: 1–8.
141. Savage E *et al.* (2005) Mumps outbreaks across England and Wales in 2004: observational study. *Br Med J* **330**(7500): 1119–1120.
142. The Global Eradication of Polio (2009) Press Release: Emergency Measures Launched in Horn of Africa to Stop Spreading Polio Outbreak. *The Global Eradication of Polio Initiative*. [Online] 24 April 2009, http://www.polioeradication.org/content/pressreleases20090422press.asp (accessed 21 November 2009).
143. Pollard AJ and Shlim DR (2002) Epidemic meningococcal disease and travel. *J Travel Med* **9**(1): 29–33.
144. World Health Organization (WHO) (2003) WHO Media Centre. *Fact sheet N°141: Meningococcal meningitis*. [Online] May 2003, http://www.who.int/mediacentre/factsheets/fs141/en/ (accessed 22 November 2009).
145. World health Organization (WHO) (2009) WHO Media Centre. *Fact sheet N°107 : Cholera*. [Online], http://www.who.int/mediacentre/factsheets/fs107/en/print.html (accessed 22 November 2009).
146. World Health Organization (WHO) (2009) WHO > Health topics > Cholera. *Global epidemics and impact of cholera*. [Online], http://www.who.int/topics/cholera/impact/en/index.html (accessed 22 November 2009).
147. Niyogi SK (2005) Shigellosis. *J Microbiol* **43**(2): 133–143.
148. Borgherini G *et al.* (2006) Melioidosis: an imported case from Madagascar. *J Travel Med* **13**(5): 318–320.
149. Aardema H *et al.* (2005) Changing epidemiology of melioidosis? A case of acute pulmonary melioidosis with fatal outcome imported from Brazil. *Epidemiol Infect* **133**(5): 871–875.
150. Lo TJ *et al.* (2009) Melioidosis in a tropical city state, Singapore. *Emerg Infect Dis* **15**(10), http://www.cdc.gov/EID/content/15/10/1645.htm (accessed 22 November 2009).
151. Weissert C *et al.* (2009) Burkholderia pseudomallei Misidentified by Automated System. *Emerg Infect Dis* **15**(11), http://www.cdc.gov/EID/content/15/11/1799.htm (accessed 22 November 2009).
152. Ricketts KD *et al.* (2008) Travel-associated Legionnaires' disease in Europe: 2006. *Euro Surveill* **13**(29): 18930, http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18930 (accessed 19 November 2009).
153. World Health Organization (WHO) (2009) *Global Tuberculosis Control – Epidemiology, Strategy, Financing. WHO Report 2009.WHO/HTM/TB/2009.411*. WHO, Geneva.
154. World health organization (WHO) (2008) WHO > Programmes and Projects > Tuberculosis (TB) > TB News – Past Home Page Features. *World health organization reports highest rates of drug-resistant tuberculosis to date*. [Online] 26 Feb 2008, http://www.who.int/tb/features_archive/drsreport_launch_26feb08/en/print.html (accessed 22 November 2009).
155. European Centre for Disease Prevention and Control (ECDC) (2009) *Migrant Health Series: Background Note to the ECDC Report on Migration and Infectious Diseases in the EU*. ECDC, Stockholm.
156. Cobelens FG *et al.* (2000) Risk of infection with Mycobacterium tuberculosis in travellers to areas of high tuberculosis endemicity. *Lancet* **356**(9228): 461–465.
157. Cruz LS *et al.* (2009) Leptospirosis: a worldwide resurgent zoonosis and important cause of acute renal failure and death in developing nations. *Ethn Dis* **19**(1 Suppl. 1): S1-37–S1-41.
158. Ricaldi JN and Vinetz JM (2006) Leptospirosis in the tropics and in travelers. *Curr Infect Dis Rep* **8**(1): 51–58.
159. Donoso Mantke O *et al.* (2008) A survey on cases of tick-borne encephalitis in European countries. *Euro Surveill* **13**(17): 18848, http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18848 (accessed 20 November 2009).
160. Steere AC *et al.* (2004) The emergence of Lyme disease. *J Clin Invest* **113**(8): 1093–1101.
161. Lo N *et al.* (2004) Emerging rickettsioses. *Parassitologia* **46**(1–2): 123–126.
162. World Health Organization (WHO) (2009) WHO > Programmes and Projects > Leishmaniasis. *Leishmaniasis, burden of disease*. [Online], http://www.who.int/leishmaniasis/burden/en/ (accessed 22 November 2009).
163. Roberts DR *et al.* (2000) DDT house spraying and re-emerging malaria. *Lancet* **356**: 330–332.
164. Armengaud A *et al.* (2008) A case of autochthonous *Plasmodium vivax* malaria, Corsica, August 2006. *Travel Med Infect Dis* **6**(1–2): 36–40.
165. World Health Organization (WHO) (2005) *Susceptibility of Plasmodium Falciparum to Antimalarial Drugs: Report on Global Monitoring: 1996–2004*, WHO Library Cataloguing-in-Publication Data. Geneva. ISBN: 92 4 159346 6.

166. Daneshvar C *et al.* (2009) Clinical and laboratory features of human *Plasmodium knowlesi* infection. *Clin Infect Dis* **49**(6): 852–860.
167. Bronner U *et al.* (2009) Swedish traveller with Plasmodium knowlesi malaria after visiting Malaysian Borneo. *Malar J* **16**(8): 15.
168. Stauffer W *et al.* (2007) Schistosomiasis. In: Barnett E.D. and Walker P.F. (eds) *Immigrant Medicine*, vol. 39, 1st edn, pp. 499–508. Elsevier, Amsterdam.
169. Sterling CR and Ortega YR (2006) Cyclospora cayetanensis: an emergent and still perplexing coccidian parasite. In: Sterling CR and Adam RD (eds) *The Pathogenic Enteric Protozoa: Giardia, Entamoeba, Cryptosporidium and Cyclospora*, vol. 8, issue 1, pp. 43–57. Kluwer Academic, Dordrecht.

Section III

Prevention and management of travel-related diseases

Chapter 12 Skin tropical infections and dermatology in travellers

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Introduction

Skin infections and tropical diseases may represent a primary condition or a secondary manifestation of illness elsewhere in the body. Cutaneous larva migrans, Madura foot and localised cutaneous simple leishmaniasis are examples of the former, whereas the latter can be exemplified by systemic conditions such as leprosy, disseminated leishmaniasis secondary to kala-azarand paracoccidioidomycosis.

The clinical approach to a patient with a tropical disease of the skin involves a thorough exercise in history taking. This must include detailed information on previous skin disease, travel history, activities while travelling, occupation, duration of signs and symptoms, evolution of clinical signs, symptoms in relatives or travel companions and a fast, practical assessment of the patient's immune status. The identification of extracutaneous signs such as fever, enlarged lymph nodes, hepatosplenomegaly and general malaise indicate systemic illness and these findings should prompt immediate action in terms of further investigations or an appropriate referral. Particular epidemiological settings in the tropics determine exposure and attack rates of specific diseases, therefore travel medicine practitioners require an understanding of the global geographical pathology and living conditions of the overseas population.

The prevalence of skin diseases in the tropics is similar to that found in developed countries and Table 12.1 summarises the main dermatological problems diagnosed in outpatients in a Latin American hospital. The main differences found in tropical dermatology when compared with the practice of this specialty in northern European hospitals are a higher incidence of endemic infectious diseases, a lower frequency of skin malignancy and the lack or decreased availability of dermatological services and travel medicine specialists. Moreover, poor living conditions, overcrowding and malnutrition account for a variety of cutaneous signs and symptoms related to poverty.

In 1997, a specialised clinic in Tropical Dermatology and Skin Infections was established at the Hospital for Tropical Diseases (HTD) in London. It provides a clinical service for travellers as well as for individuals with HIV/AIDS-related skin conditions. Our experience from this tertiary centre indicates that 75% of the total number of referrals present with a skin condition related to a travelling event. Seventy per cent of this population is represented by holiday-makers returning from the Caribbean, Latin America, India, and northern, central and eastern Africa, but cases returning from other tropical regions are also well represented. The remaining 30% of our patients travel for professional or family reasons. Only a minority of individuals included in the last group travel to the tropics to carry out aid missions, army exercises in the jungle or are immigrants who have been displaced from tropical regions of the world. The relative frequencies and most common diagnoses in travellers who have been referred to the HTD clinic are presented in Table 12.2.

This chapter presents a description of the most relevant conditions grouped by aetiological agents and the main emphasis has been placed on clinical findings and diagnosis as a practical guide to everyday work in clinical medicine. Pathogenesis of disease and management of conditions have also been included and the chapter concludes with a brief description of non-infectious skin conditions that are relevant in travel medicine.

Diseases caused by parasites, ectoparasites and bites

Cutaneous larva migrans

This common, worldwide dermatosis results from the accidental penetration of the human skin by parasitic larvae from canine and feline hosts. Cats and dogs pass ova of these helminths with their stools and larval stages develop in the

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Table 12.1 Common dermatological conditions in the outpatients department at the National Medical Centre, IMSS, Mexico City, 1993–1998

Eczema (acute, contact, chronic, stasis)
Psoriasis
Pyogenic infections
Pemphigus
Dermatophyte infections
Benign tumours
Lupus erythematosus
Viral infections
Leprosy
Leg ulcers
Drug reactions
Malignant tumours

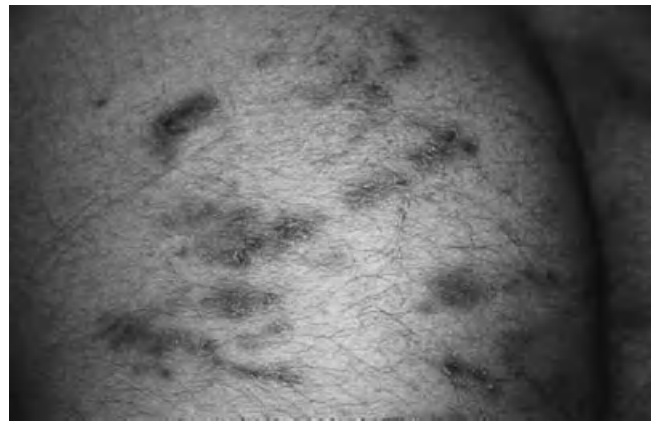

Figure 12.1 Cutaneous larva migrans acquired on a Caribbean beach. Erythematous papular lesions and serpiginous tracks in a multiple infection on the buttocks.

Table 12.2 Travel-related skin conditions in 875 patients referred to the Hospital for Tropical Diseases in London

Condition	%
Pyogenic infections	23
Eczema and eczematisation	18
Urticaria	11
Insect bites and insect bite reactions	9
Dermatophyte and other fungal infections	9
Cutaneous larva migrans	7
Leishmamasis, onchocerciasis, schistosomiasis	6
Pruritus, scabies, prurigoand other	17

soil or beach sand. A close contact with human skin allows the infective larvae to burrow into the epidermis and cause clinical disease. The main aetiological agents are *Ancylostoma brasiliensae*, *A. caninum*, *A. ceylanicum* and *A. stenocephalae*, but other species affecting ruminants and pigs can also cause human disease. Following penetration into the skin, the larvae are incapable of crossing the human epidermodermal barrier and stay in the epidermis, creeping across spongiotic vesicles, until they die a few days or weeks later. Multiple infections can last for several months.

The plantar regions of one or both feet represent the main anatomical site affected by cutaneous larva migrans, but any part of the body in contact with infested soil or sand can be involved. Individuals of all age groups and both sexes can be affected and the disease is a common problem for tourists on beach holidays where they walk on bare feet or lie on the infested sand. A report of 44 cases presenting in returning travellers attending our specialised clinic in London revealed that 70% of the lesions were located on one foot, but the buttocks were also commonly affected, as shown in Figure 12.1 [1]. The initial lesion is a pruriginous papule at the site of penetration that appears within a day following the infestation. An erythematous, raised, larval track measuring 1–3 mm in width and height starts progressing in a curved or looped fashion. New segments of larval track reveal that the organism can advance at a speed of 2–5 cm daily (unlike the 'larva currens' rash of strongyloides infection which travels at several centimetres per hour). Commonly, the larval track measures between a few millimetres up to several centimetres in the region adjacent to the penetration site, but uncommon cases may present long larval tracks surrounding large areas of the foot, with a well-defined perimalleolar distribution. Localised clinical pictures on the toes may present with only papular lesions but other presentations include blisters and urticarial wheals. Secondary complications to the presence of the parasite in the epidermis include an inflammatory reaction, eczematisation, a localised folliculitis, impetiginised tracks or papules and even deeper pyogenic infections [2]. Intense pruritus and a burning sensation are the main symptoms, although these can be variable in severity.

The diagnosis is based on the clinical history and physical findings on the affected skin. The histopathological investigation has little, if any, value in the diagnosis of cutaneous larva migrans. The study of 332 cases in central Mexico throughout 10 years in the 1980s (L.R. Orozco, personal communication, 1993) revealed that haematoxylin and eosin (H&E) preparations of affected skin show a spongiotic acute or subacute dermatitis with a variable presence of larval structures. A mild perivascular lymphocytic infiltrate was frequently observed in the dermis and a low proportion of cases may develop peripheral eosinophilia, but this is not a constant finding.

Treatment is with systemic albendazole for 3 days, at a dose of 400–800 mg daily according to body weight. Resistant cases usually respond to a single dose of 12 mg systemic ivermectin. A second and sometimes a third dose of ivermectin 1 week apart may be necessary if pruritus persists or if the larva continues to migrate 1 week after the previous dose. Cryotherapy with liquid nitrogen is rarely effective as the larvae are usually several centimetres beyond the leading edge; however, an effective topical option when oral drugs are contraindicated (e.g. very young children) is 10% tiabendazole cream applied several times daily for 10 days [3, 4].

Leishmaniasis

Leishmania spp. parasites are protozoan organisms transmitted to humans and other vertebrates by the bite of female sandflies of the genera *Phlebotomus* or *Lutzomya*. Most *Leishmania* species can cause skin or mucocutaneous disease, but a few of them affect internal organs as well. It is estimated that 15 million individuals are infected by *Leishmania* in 88 countries. There are around 20 species of Leishmania that can cause cutaneous leishmaniasis, which is the most common form of leishmaniasis. The main endemic foci are found in Asia, the Middle East, Africa, southern Europe and Latin America and from southern Texas to northern Argentina. Hot and humid environments, such as that found in rainforest jungles, provide adequate habitat for the vectors in Latin America. In contrast, desert conditions favour breeding sites for the vectors in the Middle Eastern and North African endemic regions [5]. There has been a marked increase in the worldwide incidence of cutaneous leishmaniasis observed over the past 10 years.

Following the bite from a *Leishmania*-infected sandfly, humans can heal spontaneously or else develop localised or disseminated skin disease. Sandfly and *Leishmania* species causing skin disease in humans have been classified in geographical terms as Old World and New World cutaneous leishmaniasis. Both can affect one area of exposed thin skin, but multiple infective bites or disseminated forms may present with lesions on several anatomical regions. Common inoculation sites include facial bone prominent regions, external aspects of wrists and malleolar regions. The bite of the sandfly commonly targets exposed areas, such as the external ankles during walking or medial regions of the foot when the host is at rest. Depending on the area left uncovered by light footwear, the foot dorsum, heel, toes, lateral aspect and plantar region can also be affected by bites.

Leishmania parasites can resist phagocytosis and damage by complement proteins from the host by the action of lipophosphoglycan and glycoprotein antigens. Following phagocytosis, the intracellular forms of *Leishmania* parasites induce a delayed-type hypersensitive granulomatous reaction, which adds to the tissue damage [6].

The clinical picture of cutaneous leishmaniasis has been reviewed by Chopra and Vega-López (1999). The bite of a sandfly may induce an inflammatory papular or nodular lesion of prurigo, but it may go unnoticed for several weeks. The incubation period can be as short as 15 days but commonly it is estimated at around 4–6 weeks. Certain forms may take longer to develop clinically. A non-healing papule with surrounding erythema and pain may also indicate superimposed bacterial infection, which subsequently develops ulceration. On average, 6–8 weeks after the sandfly bite a violaceous nodule with or without nodular borders starts to enlargeme and become ulcerated. The ulcer is partially or completely covered by a thick crust that, after curettage, reveals a haemorrhagic and vegetating bed. Cutaneous leishmaniasis on the upper limbs can manifest clinically as nodules covered with crust, ulceration with a raised inflamed solid border, tissue necrosis and lymphangitic forms (Figure 12.2). Advanced late forms present with scarring, skin atrophy and pigmentary changes. A particular localised form caused by *L. braziliensis* is called 'chiclero ulcer' and affects the helix of one ear (Figure 12.3), but this species commonly manifests as a single violatious ulceration of the skin (Figure 12.4). Other regions of the body surface may be affected by pigmented and hyperkeratotic lesions in a clinical form named post-kala-azar dermal leishmaniasis. This clinical form presents after an episode of visceral leishmaniasis caused by *L. donovani* in cases originating from India and Africa. All of the New World species can cause potentially severe mucosal disease; however, Old and New World skin lesions may have no morphological differences [7].

The clinical picture of cutaneous leishmaniasis and the history of exposure in an endemic region of the world

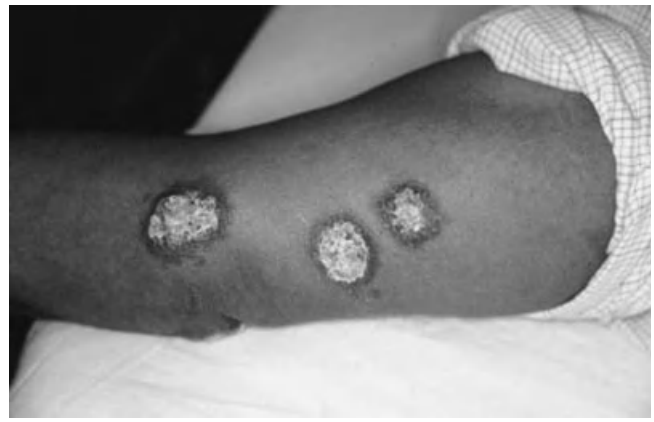

Figure 12.2 Old World cutaneous leishmaniasis from Sudan. Disseminated violaceous nodular and ulcerated lesions covered by crusts.

Figure 12.3 New World cutaneous leishmaniasis from Belize's jungle. Typical 'chiclero ulcer' with destructive inflammatory granuloma on the helix.

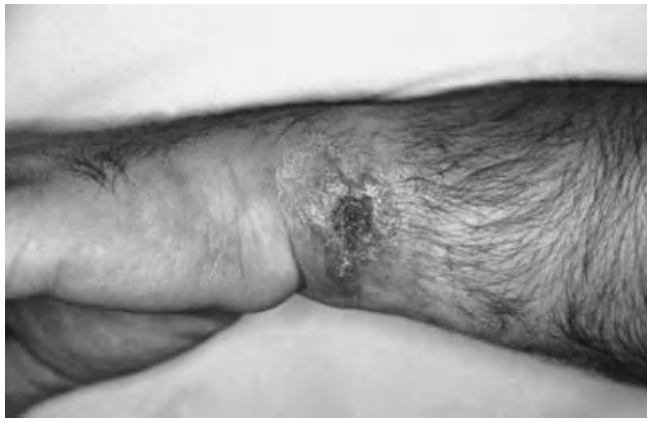

Figure 12.4 New World cutaneous leishmaniasis from Central America. Ulcerated lesion with nodular violaceous border on the external aspect of the wrist.

strongly suggest the diagnosis. Complementary tests include histology of lesional skin (granulomata are characteristic, although not diagnostic), slit-skin smears stained with Giemsa for direct microscopy (amastigotes are diagnostic) and tissue samples for culture in NNN medium and for genetic analysis by polymerase chain reaction (PCR) techniques. Culture of New World leishmania species can be difficult, however, yielding few isolates, and culture may also be less sensitive from Old World skin lesions older than 6 months [8]. PCR is twice as sensitive as culture and permits species-oriented treatment. The ultimate aim is to achieve a species-specific positive diagnosis.

The general public and health personnel in endemic areas may easily establish the diagnosis of cutaneous leishmaniasis and, following referral to a physician, one or more treatment options are available. However, in non-endemic regions and particularly in non-tropical countries, the returning traveller requires attention from a doctor experienced in dermatology, tropical medicine or infectious diseases. Several drugs are effective against *Leishmania* parasites and these include pentavalent antimonials, pentamidine, amphotericin B, triazole and allylamine antifungal compounds, and miltefosine (the first oral treatment for leishmaniasis) [9]. Intralesional injections of pentavalent antimonials, such as sodium stibogluconate (Pentostam), at weekly intervals may be sufficient for some species of Old World cutaneous leishmaniasis. However, the only effective treatment for a number of the New World species is the intravenous administration of antimonials carefully monitored in hospital and administered only by experienced personnel. In our experience, a dose of 20 mg/kg body weight daily for 3 weeks has been effective in curing most of our patients with New World cutaneous leishmaniasis caused by *L. Viannia braziliensis*. Immune response in HIV-positive patients is dependent on an adequate CD4 count [10]. Patients require long-term follow-up as leishmaniasis may relapse in rare cases. An uncommon form of lupoid leishmaniasis, also called leishmaniasis *recidivans*, may manifest several years after the original infection and present with lupoid papules or nodules on the edge of the original scar. These patients respond well to weekly intralesional Pentostam injections despite the fact that parasites are not present at the site of skin lesions.

Advice to travellers about the use of insect repellents and control of domestic animals are the main areas to address regarding protective measures against leishmaniasis.

Onchocerciasis

This filarial disease is acquired through the inoculation into the skin of *Onchocerca volvulus* by blackflies of the genus *Simulium*. This infection, also named 'river blindness', is highly prevalent in Africa within latitudes 15°N and 15°S, Yemen, and also affects tropical countries in Central and South America. Fast-flowing brooks and small rivers provide breeding sites for the blackfly vectors and only the female individuals are haematophagous. They can bite potential hosts throughout the day, principally those pursuing outdoor activities. Holiday-makers as well as those travelling for professional reasons risk acquiring this parasitic disease, but it

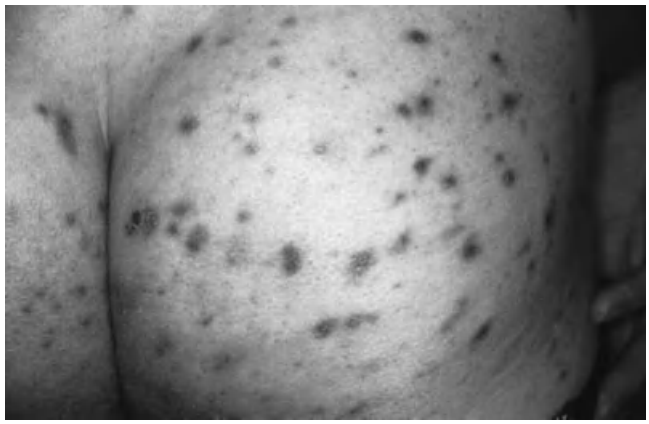

Figure 12.5 Onchocerciasis from Central Africa. Erythematous and pruriginous papules and nodules on the buttocks.

is the local population that suffers the highest toll from both clinical disease and subsequent disability.

Following an approximate incubation period of 1 year, the adult worms live freely in the skin or within fibrotic nodules or cysts named onchocercomas. The female adult worm releases microfilaria into the dermis, which are disseminated by the lymphatic system. Adult worms may live and reproduce for up to 15 years in the human host.

The main clinical manifestations include pruritus and skin lesions, consisting of lichenified plaques, papular or prurigo eruptions, nodules, atrophic changes and pigmentary abnormalities. Early symptoms include fever, arthralgia and transient urticaria affecting the face and trunk. Pruritus and scratching lead to eczematisation, revealed as patches of lichenified and excoriated skin on the trunk and lower limbs. The buttocks are commonly involved (Figure 12.5) and oedematous plaques are characteristic in Latin American cases, named locally 'mal morado'. Late skin lesions show atrophy and hyper- and hypopigmented patches, giving the appearance of leopard skin described in African cases. The presence of filaria in the ocular anterior chamber causes acute symptoms and late ocular lesions lead to blindness.

The parasitological diagnosis includes the identification of microfilaria in samples taken from skin snips from the back, hips and thighs (which is highly specific, although not particularly sensitive for early or light infections), day and night blood samples for microfilaria, specimens for histopathological and PCR investigation and serology (although serology cannot distinguish between current and past infections). Most patients develop a peripheral hypereosinophilia. If these tests are negative but onchocerciasis is still strongly suspected, the Mazzotti test can be performed. This is positive if there is an increase in pruritus 24–48 h after administration of oral (or topical [11]) diethylcarbamizine. The Mazzotti test must only be performed on patients with no eye lesions, as there may be a risk of loss of visual acuity.

Ivermectin at standard doses of 200 μg/kg arrests microfilarial production, but does not fully kill the adult worms [12]. As the adult worms can live for up to 14 years, ivermectin is given at annual intervals to prevent disease progression. The surgical excision of nodules is also indicated and all patients require specialised attention in tertiary medical centres, including a comprehensive ophthalmological assessment. An active programme of mass therapy for individuals living in endemic regions of the world has been in place for more than a decade, with the treatment of choice in endemic areas being an annual [13] single dose of 150 μg/kg systemic ivermectin. The safety of ivermectin in pregnancy has not yet been established. Recent evidence suggests that doxycycline, given at a dose of 100 mg/day for 6 weeks, may have a microfilaricidal effect of longer duration and also has a moderate macrofilaricidal effect on adult worms [14]. Ivermectin remains the drug of choice in endemic areas, owing to the long duration of administration for doxycycline; however, doxycycline may be an alternative in non-endemic areas on the basis of its longer-term interruption of embryogenesis (WHO 2007).

Gnathostomiasis

A number of *Gnathostoma* species live as adult worms in the intestine of domestic cats, dogs and other fish-eating mammals. Travellers can acquire the disease as accidental hosts by eating contaminated, uncooked fish, shellfish, frogs, chicken, cats or dogs. The larval stages do not reach maturation in the human body and can cause disease in several internal organs as well as in the skin. The disease is prevalent in South and Southeast Asia, China, Japan, Indonesia, central and South America, and particularly in Mexico (due to the consumption of raw fish marinated in lime called 'ceviche').

Episodes of intermittent migrating subcutaneous oedema (localised or not localised) with pruritus constitute the main clinical picture and cases can adopt a chronic protracted course for years. The episodes of oedema can be quite inflammatory and painful, and the larvae can erupt from the affected skin. The feet are not commonly affected. The differential diagnosis may include the calabar swellings and ocular migration of Loa Loa infection; however, the geography of travel should enable this distinction. A marked eosinophilia usually develops as the larvae penetrate the gastrointestinal wall, but subsides as the chronic stage begins and the larvae enter the subcutaneous tissues. The triad of eosinophilia, migratory lesions and obvious risk of exposure is highly suggestive of gnathostomiasis; however, the absence of eosinophilia should not exclude the diagnosis. Confirmation of the diagnosis is made with serology.

For many years the surgical extraction of the larva from the skin represented the curative therapeutic approach [15], however a trial by Kraivichian *et al.* in 1992 confirmed the efficacy of albendazole in humans, with cure rates of >90% at a dose of 400 mg bd for 21 days [16]. Small studies of ivermectin 0.2 mg/kg either as a stat dose or doses on two consecutive days seem to show similar efficacy to albendazole [17]. Initial treatment is not always successful and second courses of treatment have been needed in some cases, either with albendazole or ivermectin. Further trials are needed to determine whether relapse rates are lower with combination drugs than with monotherapy [18].

Loa Loa

Loa Loa is a filarial helminth infection transmitted in the Central African rainforests by bites from the Chrysops fly. It can affect the skin and eyes.

As the larvae mature they migrate away from the bite site around the body in the subcutaneous tissues or deep fascial layers, at intervals producing transient, itchy oedematous lumps called Calabar swellings. These can last from between a few hours to a few days. Some patients may present with recurrent migratory angio-oedema [19]. Adult worms may be clearly visible migrating beneath the conjunctiva. Diagnosis is made by following clinical, parasitological or serological methods. Microfilaria may be found on a blood smear collected around midday. Eosinophil count may be normal initially. Symptoms may not appear until several years after the patient has left an area of endemicity [20].

The surgical removal of adult worms may be possible. The microfilariae can be treated with diethylcarbamazine or ivermectin at standard doses of 150 µg/kg; however, there is a risk of severe neurological reactions such as meningoencephalitis or encephalopathy due to dying microfilaria in patients with a high microfilaraemia load. Recent studies have shown that doxycycline 100 mg bd for 6 weeks will produce a more gradual reduction of microfilaria [21].

Trypanosomiasis

African trypanosomiasis is a protozoal parasitic infection occurring in tropical parts of Africa transmitted by the bite of the tsetse fly. It causes a neurological disease also known as sleeping sickness, but the initial bite can produce a pruritic or painful inflammatory reaction at the site of inoculation called a chancre. This is characteristically an indurated red or violaceous nodule 2–5 cm in diameter that usually appears 48 hours after the bite and is accompanied by regional lymphadenopathy. A central necrotic eschar may form before the chancre desquamates within 2–3 weeks, leaving no trace. Many patients think of it as an isolated 'boil'. Chancres are rare in *Trypanosoma gambiense* but occur in 70–80% of people infected with *Trypanosoma rhodesiense*. Erythematous, urticarial or macular rashes on the trunk called trypanids, which may have a haemorrhagic component, may occur in up to 50% of light-skinned individuals 6–8 weeks after the onset of illness. Diagnosis requires the identification of the parasite in blood, lymph nodes or cerebrospinal fluid (CSF). Suramin is the drug of choice for the early haemolymphatic stage, but once involvement of the central nervous system (CNS) has occurred, melarsoprol, an arsenical, then becomes the drug of choice as this penetrates the blood–brain barrier.

South American trypanosomiasis, also known as Chagas disease, occurs in Central and South America due to transmission of *Trypanosoma cruzi* from the bite of triatomine bugs in poor, rural areas. The domestic cycle is the result of human invasion in wild areas, where the vector bugs invade mud huts or shacks with crude wooden walls or palm leaf roofs in search of a blood meal. They are also known as 'kissing bugs' due to their habit of biting human faces, and the parasite penetrates the skin wound or conjunctiva, leaving a local inflammatory lesion. When *T. cruzi* penetrates through the conjunctiva the local periorbital swelling with conjunctivitis and local lymphadenopathy is referred to as Romana's sign. When entry occurs through the skin wound, the erythematous or violaceous furuncle-like area of induration is called a chagoma. This may last for several weeks and be accompanied by regional lymphadenopathy. Other signs include fever, malaise, headache, myalgia, hepatosplenomegaly and transient skin rashes. The main organs affected in Chagas disease are the heart, oesophagus and intestine, although the CNS can also be invaded. Acute myocarditis may lead to cardiac insufficiency, and the chronic stages can cause cardiomegaly and severe heart failure. Diagnosis requires a history of exposure to *T. cruzi* and in the early stages microscopy for identification of the parasite. In the later stages culture, serology, PCR or xenodiagnosis are required. Treatment is difficult, but in the early stages nifurtimox and benznidazole are used for a period of 30–90 days [22].

Tungiasis

Tungiasis is a localised skin disease commonly affecting one foot and caused by the burrowing flea *Tunga penetrans*. This is also known as chigger infestation, jigger, sandflea, chigoe and puce chique (Fr.). It has been reported that this flea originated in Central and South America [23] and was subsequently distributed in Africa, Madagascar, India and Pakistan. It is a very small organism, approximately 1 mm in length, and lives in the soil near pigsties and cattle sheds, and in sandy soil of deserts and beaches. Fecundated females

require blood and their head and mouthparts penetrate the epidermis to reach the blood and other nutrients from the superficial dermis. After taking nourishment for several days, eggs are laid on to the exterior surface and the flea dies.

These fleas commonly affect one foot, penetrating the soft skin on the toe web spaces, but other areas of toes and plantar aspects on the foot can be affected [24] and rarely other parts of the body such as the buttocks, thighs or hands [25]. The initial burrow and the flea body can be evident in early lesions but within 3–4 weeks a crateriform single nodule develops, with a central haemorrhagic point. Superimposed bacterial infections may be responsible for impetigo, ecthyma, cellulites and gangrenous lesions. The diagnosis is made clinically but skin specimens for direct microscopy and histopathology with H&E stain reveal the structures of the flea and eggs.

If embedded sand-fleas are not removed early, superinfection is the rule [26]. Curettage, cryotherapy, surgical excision or else careful removal of the flea and eggs are the curative therapeutic choices. Early treatment and avoidance of secondary infection are of the utmost importance in all infested travellers and particularly in individuals with diabetes mellitus, leprosy or other debilitating conditions of the feet. Tetanus prophylaxis should be up to date. A haemorrhagic nodule caused by *T. penetrans* may pose differential diagnostic difficulty with an inflamed common wart or a malignant melanoma, but the short duration of the lesion and the history of exposure indicate the acute nature of this parasitic disease.

Myiasis

A number of diptera species in larval stages (maggots) may colonise the human skin. Species of *Dermatobia* and *Cordylobia* are the commonest found in the tropics, respectively in the Americas and Africa, whereas European cases originate from *Hypoderma* spp. [27]. Dermatobia larvae develop from fly eggs carried to the human by a biting mosquito, whereas Cordylobia larvae penetrate the skin after hatching from eggs deposited on moist soil, or clothing and bed linen hung to dry outdoors that has not been ironed. A local inflammatory reaction to the larvae, with secondary infection, is responsible for the signs and symptoms of disease.

The cutaneous lesion is a 1–2 cm furuncle-like lesion with a central punctum through which serosanguinous or purulent fluid discharges. The patient may complain of a crawling sensation within the lesion and movements of the larvae may be seen within the central punctum. Elderly and debilitated individuals of both sexes with exposed chronic wounds or ulcers have a particularly high risk of suffering from this infestation. Furunculoid and subcutaneous forms may affect any part of the body, but in children the scalp is a commonly affected site. Chronic ulcers of the lower legs and feet represent a predisposing factor and myiasis often complicates severe infections by bacteria or fungi. Larvae feed on tissue debris and may not cause discomfort or symptoms at all. Cases are observed throughout the year in tropical regions where the standards of hygiene, nutrition and general health are poor, although myiasis in this setting is rarely seen in the returning traveller. The diagnosis is based on clinical suspicion and physical findings.

The treatment of choice is the mechanical removal or surgical excision of the larvae [27]. Single furunculoid lesions can be covered by thick petroleum jelly or paste to suffocate the larvae, which can then be extracted. Superficial infestations respond to repeated topical soaks or baths in potassium permanganate, at a 1:10,000 dilution in water, carried out for a few days. Cases with secondary pyogenic infection require a full course of β-lactam or macrolide antibiotics. Unsuccessful occlusive therapy may necessitate sterile surgical extraction and debridement (Hochedez P, Caumes E 2008).

Scabies

Scabies is a cosmopolitan problem but individuals in poor tropical countries with low standards of hygiene, and particularly overcrowding, can suffer from cyclical outbreaks. Travellers often acquire this infestation by personal contact, or from infested clothes, towels or linen (Ectoparasites 2004). The human scabies mite *Sarcoptes scabiei* commonly affects the skin of both feet of infants and children. Adults rarely manifest scabies on the lower limbs below the knees (Hebra lines), but exceptional cases of crusted or Norwegian scabies may present with lesions on both feet. It usually spares the face and head. The scabies mite burrows a tunnel of up to 4 mm into the superficial layer of the epidermis, where eggs are laid. The eggs hatch and reach the stage of nymph, and subsequently become an adult male or female mite. Female individuals live for up to 6 weeks and lay up to 50 eggs. A new generation of fecundated females penetrates the skin in regions adjacent to the nesting burrow, but the mite infestation can also be perpetuated by clothes, or by reinfestation from another host in the family.

Pruritus usually occurs within 3 weeks of contact and is often worse at night. Papules, with or without excoriation, and S-shaped burrows are the elementary classical lesions of scabies. Infants and young children present with papular, vesicular and/or nodular lesions on both plantar regions, but other parts of the feet can be affected. In contrast, adult travellers present with bilateral lesions on the interdigital web spaces of the hands, upper limbs, anterior axillary lines, periumbilical region, external genitalia and buttocks. Travellers of all age groups suffering from chronic crusted scabies

may present with eczematisation, impetiginised plaques and hyperkeratosis, masking the typical clinical signs of this infestation. Large crusts covering inflammatory papular lesions contain a large number of parasites and a careful examination is required to prevent health personnel from acquiring the infestation.

A suspicion of scabies should be raised in any individual with intense pruritus. Pruritus in family members may be a supportive clue. The clinical findings support the diagnosis. Confirmation is obtained by direct microscopy of skin scrapings from a fresh, non-excoriated burrow, revealing the structures or faecal pellets of the mite. This test is carried out on a glass slide in 10–15% potassium hydroxide solution under low power, it has a low sensitivity if carried out by inexperienced hands.

Topical treatment overnight with benzyl benzoate, malathion, 1% lindane or 5% permethrin, lotion or cream, is usually effective. A second course is recommended 1 week after the original application and all the affected members of a household or travelling party require treatment at the same time to prevent cyclical reinfestations. Severe cases or individuals in particular community settings, such as those living in homes for the elderly, orphanages, prisons or psychiatry wards, require oral treatment with a single dose of ivermectin. Severe outbreaks often require a second dose of ivermectin after a 2-week interval (200 μg/kg of body weight). Safety data for ivermectin in pregnancy and lactation is to date unclear. The intensive use of antiscabietics has led to some reports of drug resistance [28]. Other therapeutic measures are directed to controlling the symptoms, inflammation and infection. Clothes and bed linen require washing at high temperature to kill all young fecundated females but a number of authors have demonstrated that this is not necessary. In the right epidemiological context, scabies may represent a venereal disease. Pruritus may last for several weeks after cure. Post-scabies eczema, due to the irritant effects of topical treatments, is the most frequent complication and can be mistaken for drug failure or reinfestation. Most recurrences are due to reinfection from untreated contacts [29].

Ticks

Ticks are cosmopolitan ectoparasites capable of transmitting severe viral, rickettsial, bacterial and parasitic diseases. The transmission of infectious agents takes place at the time of taking a blood meal from a human host, who becomes infested accidentally. Tick paralysis is a rare, acute, ascending flaccid paralysis that can occur within days following the bite and is thought to be due to proteins injected into the human host during blood feeding. Some of the pathogens that can be transmitted by ticks include the arbovirus for Crimean-Congo haemorrhagic fever or tick-borne encephalitis virus, bacteria such as those causing relapsing fever, Lyme disease, ehrlichiosis, babesiosis and tularaemia, and numerous rickettsia, which may cause Rocky Mountain spotted fever, Mediterranean spotted fever, African tick bite fever, Far Eastern spotted fever, tick-borne lymphadenopathy or tick typhus. Ticks may carry more than one pathogen and individuals may develop co-infections from a bite. Co-infection may increase disease severity and duration.

Figure 12.6 Tick bite from Western Africa. Erythema and characteristic eschar in a patient who subsequently developed typhus.

The bite of a tick is painful and the patient may be aware of this episode. Infestation may present as erythematous pruritic papules, which on closer inspection may reveal partially embedded ticks. The bite produces a local inflammatory reaction suggesting initially an ordinary papular insect bite that subsequently causes localised superficial vascular damage with necrosis. The characteristic clinical picture manifested as an eschar can be easily recognised on careful physical examination (Figure 12.6). An area of circular scaling of the skin surrounding the original haemorrhagic bite can be seen after a week or 10 days. Residual chronic lesions may leave hyperpigmented patches with a central induration. Tick bites may be associated with local secondary bacterial infection at the site of the bite, foreign body granuloma due to retained mouthparts, local irritant or allergic contact dermatitis and, rarely, anaphylaxis, either due to the bite itself or to the removal of the feeding tick. Bites due to soft ticks may result in necrotic ulceration, vesiculobullous lesions or even significant oedema involving an extremity.

Removal of the tick can be carried out using forceps, avoiding compression of the body, as squeezing may result in a bolus injection of saliva. Suffocation of the tick with petroleum jelly should be avoided as delay in tick withdrawal allows increased time for possible pathogen transmission.

Careful follow-up and self-surveillance is indicated as systemic illness may start a few days or weeks following the tick bite. Symptoms such as a fever, skin rash, lymphadenopathy, fatigue and night sweats indicate systemic disease, and the patient requires referral to a hospital physician or to a specialist in tropical or travel medicine. Antibiotics, if indicated, should be started early in the course of illness to prevent the development of chronic or serious infection. If infected individuals are not improving with initial treatment, co-infection should be considered [30].

Fleas

The common human flea *Pulex irritans* is cosmopolitan, but a number of other species show preference for tropical climates. Such is the case of the tropical rat flea *Xenopsylla cheopis*. Fleas bite humans to get a blood meal and in doing so produce a localised inflammatory reaction. History of exposure can reveal an individual host or family members recently moving house or acquiring a second-hand piece of wooden furniture, in which fleas can live for months without taking blood meals. Fleas may be the vectors of plague and typhus fever, and, like the human body louse, some may also transmit bartonella, the agent of trench fever, cat scratch disease, endocarditis and bacillary angiomatosis [31, 32].

A clinical picture of prurigo with papules, vesicles or small nodules on both feet and lower legs is characteristic and the lesions are often found in clusters (Figure 12.7). Such papular urticaria is most often caused by fleas or bedbugs, although almost any arthropod is capable of inducing this reaction [33]. The papular discrete lesions may reveal a central haemorrhagic punctum and the lesions in clusters often show a remarkable asymmetry. Modification of the initial pruriginous lesions may result from intense scratching and superimposed secondary bacterial infection.

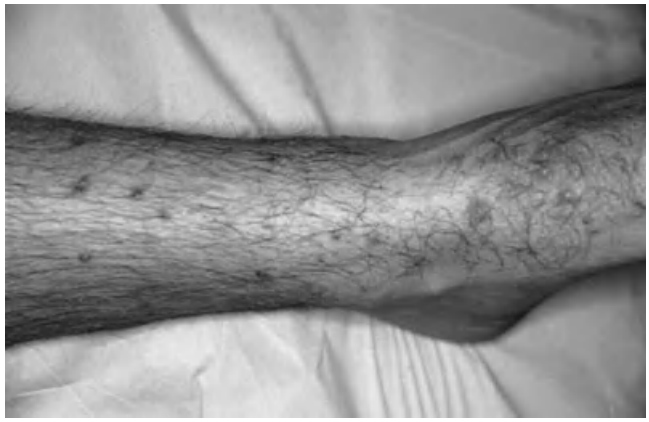

Figure 12.7 Bites by *Pulex irritans* in a traveller. Clusters of erythematous and pruriginous papules on the lower limbs.

Fumigation can be successfully achieved by using common insecticide products approved for domestic use. Severe reactions of prurigo require a topical steroid cream and impetiginised cases topical or systemic antibiotics. Antihistamine lotions or tablets may provide symptomatic relief. Severe cases are treated with a single dose or short course of systemic corticosteroids.

Bedbugs

The common bedbug *Cimex lectularius* hides during the day in cracks and crevices of walls or thatched roofs and feeds at night, often inflicting three or more bites in a row ('breakfast, lunch, dinner'). Bites are typically arranged in clusters or a linear fashion and vary from urticated wheals to haemorrhagic blisters. There is no evidence for disease transmission by bedbugs [34].

Spiders

Bites from a number of species of spider can result in severe local necrotic reactions, which may sometimes require extensive debridement and can be associated with disseminated intravascular coagulation or tetany.

Fire ants

Fire ants swarm when their mound is disturbed and multiple stings typically occur simultaneously. A burning sensation lasts for several minutes and is frequently accompanied by wheals. Sterile pustules then develop, which are extremely pruritic but non-tender. The presence of tenderness suggests secondary infection. Potent topical steroids can help to relieve itching. Anaphylaxis may occur in those sensitised by previous stings [35].

Blister beetles

These are distributed worldwide. Blister beetle dermatosis comprises extensive erythema, vesicles, pustules and sometimes bullae. Epidemics of bullous disease in hospital wards have been described in tropical climates where windows are left open at night. 'Nairobi eye' or 'night burn' is due to a blister beetle found in Northern Kenya [36].

Centipedes and millipedes

Centipedes can inject a venom that can result in self-limiting pain, paraesthesia, erythema, oedema and profuse bleeding. Their bite often has a characteristic chevron shape. Millipedes lack venom, but secrete caustic substances, particularly

when trapped in clothing, that may result in local burns or deep brown discoloration of the skin.

Caterpillars

Cutaneous, corneal or aerosol contact with the urticating hairs from a variety of cocoons, caterpillars and moths can cause a localised dermatitis (erucism), systemic reactions (lepidopterism) or migratory inflammatory polyarthritis (dendrolimiasis). Lepidopterism is characterised by generalised urticaria, headache, conjunctivitis, pharyngitis, nausea, vomiting, bronchospasm, wheezing and, rarely, dyspnoea or anaphylaxis. Dendrolimiasis is characterised by an urticating maculopapular dermatitis, migratory inflammatory polyarthritis or polychondritis, chronic osteoarthritis and, rarely, acute scleritis [37, 38].

Freshwater and sea water conditions

Cercarial dermatitis (swimmer's itch) is caused by penetration of the skin by the free-living larval stages of the helminth schistosomiasis in freshwater lakes. It occurs in sub-Saharan Africa, Southeast Asia and also parts of Brazil and Venezuela. With an itchy, papular rash, history of freshwater swimming and eosinophilia, serology should be considered [39].

Travellers may sustain injury after exposure to a marine environment as a result of envenomation, secondary infection, or allergic or contact dermatitis. Injury may be due to jellyfish, coral reefs, anemones, sea urchins and venomous fish. The returning traveller may commonly have post-inflammatory lesions characterised by hyperpigmentation and scarring. Seabather's eruption is a relatively common dermatitis that occurs after swimming in sea water. Larvae of particular sea anemones become trapped in the bathing suit or wetsuit and pressure results in toxin release. Pruritic, monomorphic, erythematous papules or vesicles develop within hours on areas that were covered by the bathing suit, and new lesions may continue to occur for days after the initial exposure. The rash may persist for up to 2 weeks. Treatment is symptomatic, including topical steroids [40].

Bacterial infections

Pyogenic infections

Common bacterial skin infections affecting the traveller are caused by *Staphylococcus* and *Streptococcus* species. These infectious agents are ubiquitous in both urban and rural environments and are capable of causing disease in travellers of all age groups. Healthy and immunocompromised hosts develop pyogenic infections of the skin following direct inoculation of bacteria. Less often, haematogenous dissemination and even a septicaemic state may develop as a result of a minor skin injury. The port of entry for these pathogenic organisms is often unnoticed by both the traveller and doctor, but minor injuries, insect bites, friction blisters or superficial fungal infection are the commonest found in clinical practice. Other clinical circumstances such as burns and surgical procedures also play a role as risk factors for these infections.

Pyogenic bacteria cause damage in the infected tissue by the pathogenic action of proteases, haemolysins, lipoteichoic acid and coagulases. Erythrogenic toxins are responsible for the erythema commonly observed in infections by *Streptococcus* spp [41].

The clinical spectrum of skin pyogenic infections includes folliculitis (Figure 12.8) and furuncle and carbuncle formation on areas with hair follicles, to abscess formation, cellulitis (Figure 12.9) and necrotic ulceration at the more

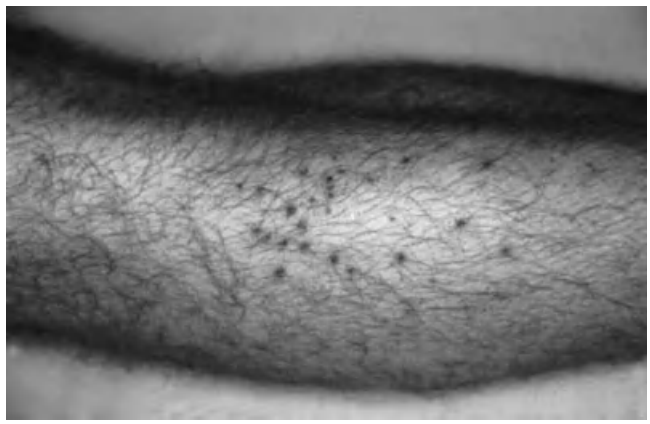

Figure 12.8 Folliculitis on lower limbs. Erythematous and excoriated follicular papules.

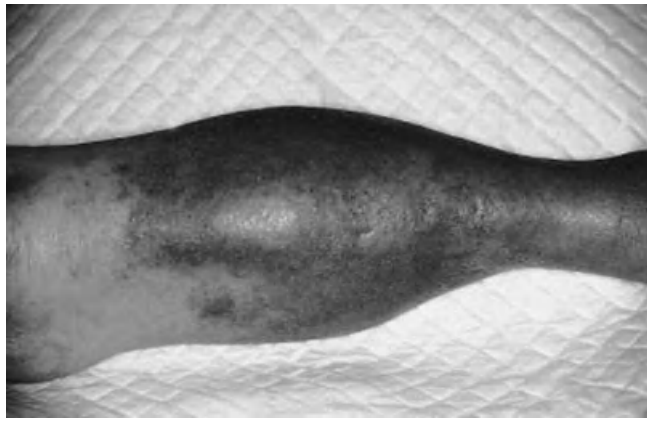

Figure 12.9 Cellulitis on the leg of an elderly traveller. Localised plaque of shiny erythematous skin with dermal thickening.

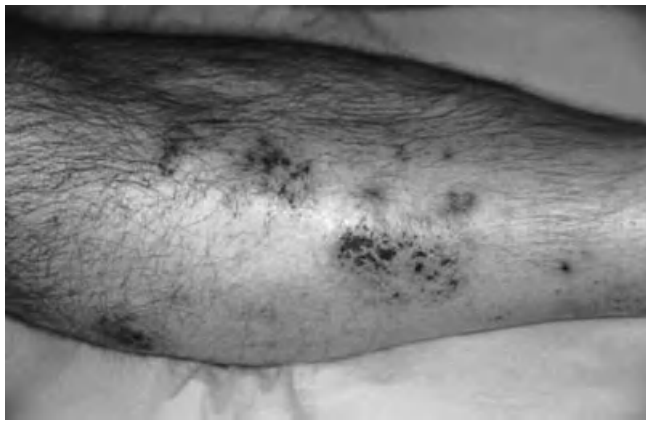

Figure 12.10 Impetigo in a returning traveller. Plaques with erythema and yellowish thin crust showing superficial excoriation.

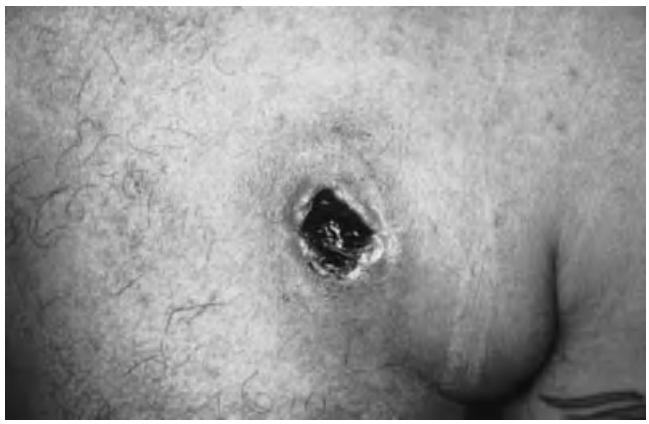

Figure 12.11 Ecthyma on the chest of a backpacker. Pyogenic ulcer following a friction blister caused by the strap of a rucksack.

severe end of the spectrum. Plaques of impetigo and infiltrated thickened dermis commonly affect the lower limbs (Figure 12.10) and are respectively caused by *Staphylococcus* and *Streptococcus* species. The perimalleolar regions are by far the most commonly affected areas of the foot as they are exposed to mechanical trauma while travelling. The dorsum, toes and heels follow in frequency.

Common clinical signs of pyogenic infections include a variety of manifestations such as erythema, inflammation, pus discharge, abscess formation, ulceration, blistering, necrotising lesions and gangrene. Severe scarring may result from pyogenic ulcers caused by friction injury (Figure 12.11). Most pyogenic skin infections in the traveller are painful and the diagnosis is based on the clinical history and findings.

Bacteriological investigations and antibiotic sensitivity profiles to must be carried out if available. Disseminated, chronic or severe infections require an immediate referral to a dermatologist or to an infectious disease specialist. Uncommon cases of streptococcal infection of the throat may express

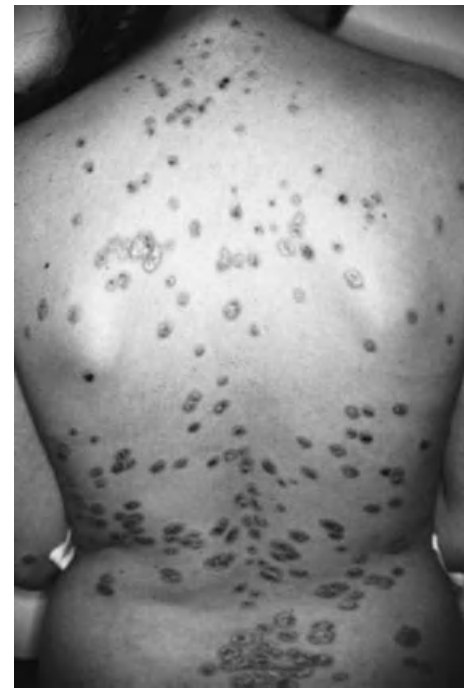

Figure 12.12 Guttate psoriasis on the back. Sudden eruption in a young traveller, characterised by erythemato-scaling 'drops' and small plaques.

clinically with a sudden eruption of guttate psoriasis as a result of bacterial superantigen stimulation (Figure 12.12).

Mild infections are successfully treated with bathing or soaking of the affected skin in potassium permanganate solution (1:10,000 dilution in water) for 15 minutes daily. Other mild superficial infections, such as isolated plaques of impetigo or impetiginised eczema, respond well to antiseptic or antimicrobial creams and ointments containing cetrimide, chlorhexidine, fucidic acid or mupirocin. Acute or chronic eczema require treatment with potent topical steroids to eliminate risk factors for infection. Infections with multiple lesions, or those involving larger areas of the skin, require a complete course of systemic β-lactam or macrolide antibiotics in addition to the above topical treatments. Recurrent episodes of cellulitis require longer courses of these antibiotics, and hospitalisation followed by surgical debridement is mandatory in necrotic lesions, gangrenous plaques and deeper infections with severe fasciitis. Superficial infections of the foot skin complicated by deeper involvement with necrosis of soft tissues carry a high mortality rate of up to 25% [42].

Treponemal infections

Syphilis is an infection caused by *Treponema pallidum*, which remains common worldwide [43]. Primary syphilis has an

incubation period of 9–90 days, during which serology may not yet be positive, but diagnosis can be made by demonstrating the organism on dark ground microscopy. Secondary syphilis presents with an asymptomatic, symmetrical papular eruption and scaling of plantar regions. Other clinical features such as concurrent palmar involvement, as well as the history of a primary chancre and the characteristic trunkal rash while travelling, confirm the clinical suspicion of infection. The rash can vary however and patients co-infected with HIV may present atypically [44, 45]. A definitive diagnosis can be established by specific tests such as positive dark-field microscopy from early skin lesions, as well as from highly sensitive treponemal serology. Despite the fact that syphilis is not strictly a tropical disease, it represents a significant problem for the returning traveller involved in high-risk sexual activities while in the tropics [46]. The treatment of choice is penicillin, but allergic individuals respond to erythromycin or tetracyclines [47].

Yaws is a non-venereal treponemal tropical disease manifesting on the feet and periorificial skin on the face. This condition affects mainly the male rural population in South America, sub-Saharan Africa and Southeast Asia. It is associated with poverty in the humid tropics [48] and one of the characteristic clinical presentations is that of plantar hyperkeratosis. Late tertiary infection results in asymptomatic palmoplantar keratoderma that develops nodular hyperkeratosic lesions, leading to painful disability; hence the characteristic walk known as 'crab yaws'. The clinical picture can be difficult to differentiate from other types of infectious and non-infectious plantar keratodermas. Unlike syphilis, late lesions of yaws are thought to be limited to the skin, bones and joints. Transmission occurs through direct person-to-person contact from ulcerative lesions via wounds and abrasions. Tests for diagnosis include dark-field microscopy of early lesions and treponemal serology, although these results may be identical to those for syphilis and distinguishing these infections can only be done clinically [49]. The treatment of choice is penicillin, but *Treponema pallidum pertenue* also responds to tetracyclines and macrolides [50].

Other bacterial infections in the traveller

Tropical ulcer is a single painful, rapidly growing, sloughing ulcer, usually on the leg. It is a polymicrobial infection, often precipitated by trivial trauma such as a scratch or insect bite. It is usually superficial, with undermined, violaceous edges. The ulcer may reach several centimetres in diameter after a couple of weeks. Important differential diagnoses include cutaneous leishmaniasis, atypical mycobacteria and pyoderma gangrenosum. Smears taken from the base and edges of the ulcer may identify the infecting organisms. Imaging may detect underlying bone involvement [51]. Treatment options include tetracycline (500 mg qds for 7 days) plus metronidazole (250 mg tds for 10 days). Surgery may be required for chronic ulcers [52].

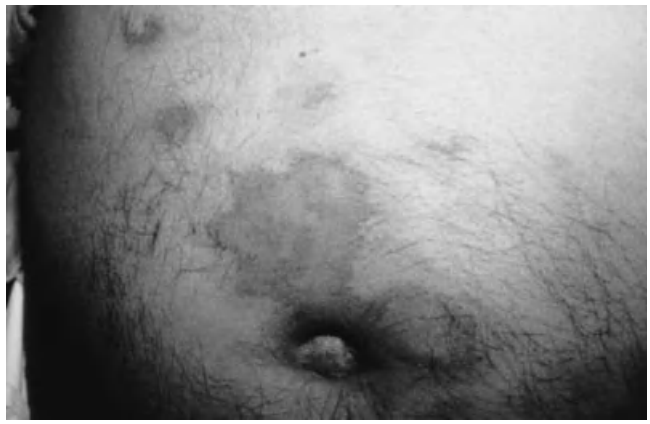

Figure 12.13 Fatal septicaemia by *Vibrio vulnificus* from the Gulf of Mexico. Violaceous and purpuric patches affecting abdominal skin.

Where a marine route of entry of bacterial infection is suspected, the spectrum of infective agents must include Gram-negative bacilli such as *Vibrio vulnificus* [53]. Tropical seaborne infections by halophilic *Vibrio vulnificus* can produce localised or systemic disease manifested by acute and painful erythema, purpura, oedema and necrosis, particularly affecting the lower limbs. Cases of returning travellers presenting in inland metropolitan areas can be very difficult to diagnose and these patients carry a high mortality risk. Fatal septicaemia manifests with coalescing purpuric patches on one or both lower limbs that subsequently spread to the periumbilical region (Figure 12.13). The infection is acquired by direct traumatic inoculation in estuaries and sea waters, or by ingestion of raw seafood, particularly oysters. Male individuals with a history of liver disease and iron overload states are the group at highest risk for this infection [54]. Severe cases require immediate referral to a specialist hospital physician, as intravenous antibiotics and early surgical debridement represent the treatment of choice.

Exfoliation of the plantar skin is part of the complex and severe picture in cosmopolitan cases with staphylococcal scalded-skin syndrome (SSSS) [55], whereas necrotic ulceration of the foot can result from tropical cutaneous diphtheria caused by *Corynebacterium diphtheriae* [56]. Cutaneous diphtheria commonly manifests as a non-healing, single ulcerated lesion on the toe or toe cleft, lasting between 4 and 12 weeks. Numerous other bacterial infections may also rarely afflict the traveller, such as cutaneous bartonellosis [57].

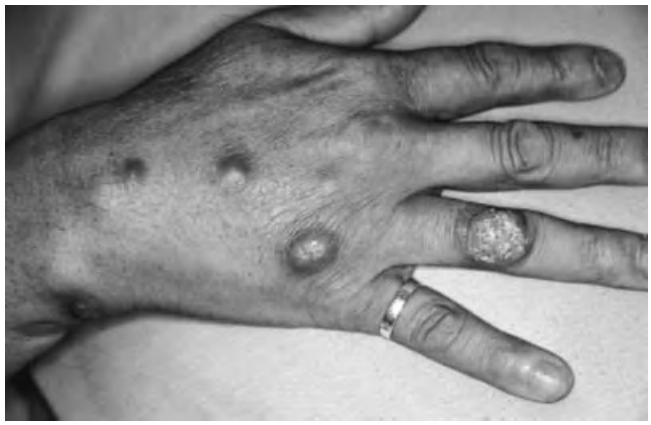

Figure 12.14 *Mycobacterium marinum* infection of the hand in a patient from Hong Kong. Fish-tank granuloma with violaceous nodules showing proximal lymphangitic dissemination.

Mycobacterial infections

Several mycobacterial species can cause primary or secondary infection in the traveller. The 'swimming' or 'fishtank granuloma' is an infection caused by *Mycobacterium marinum* (Figure 12.14). Other common chronic mycobacterial tropical infections include leprosy, tuberculosis and Buruli ulcer, but these conditions are not relevant for travellers. They are caused by *M. leprae*, *M. tuberculosis* and *M. ulcerans* respectively. Mycobacterial skin diseases can be acquired by direct skin contact with a patient, by direct accidental or occupational inoculation and by inhalation of the infective organisms. Particular clinical forms of cutaneous tuberculosis result following haematogenous dissemination from a primary infection elsewhere. The respiratory route is particularly important for leprosy and diverse forms of pulmonary tuberculosis. In the case of Buruli ulcer, contact with infected water in rural areas of Africa may represent the main source of infection. A toxin called mycolactone seems to be responsible for the severe tissue destruction and ulceration seen in patients with Buruli ulcer [58]. In general, however, it is accepted that agents causing mycobacterial skin diseases have a low pathogenic potential as most infected individuals in endemic regions do not develop clinical mycobacterial diseases.

Mycobacteria are very complex organisms, most of them ubiquitous in nature as saprophytes, but a number of species cause disease in other animals. A very thick wall surrounds the cytoplasmic membrane of mycobacteria, which contains virulence factors such as proteins and glycolipids. Mycobacteria can inhibit efficient phagocytosis and intracellular killing by macrophages and also interact with the host's immune cells. This interaction results in chronic inflammation, tissue damage and immunopathology, all of which account for the signs and symptoms observed in the wide range of mycobacterial diseases.

Management and treatment of mycobacterial infections

All mycobacterial diseases require highly specialised diagnostic investigations that in many cases can only be carried out in a tertiary hospital setting. Most mycobacterial diseases affecting the skin represent public health priorities, not only for the endemic countries where they occur but also at an international level, as established by the World Health Organization (WHO). Following the diagnosis of individual cases, a long-term multidrug therapeutic regimen can be prescribed only by specialised physicians. Mycobacteria are known to develop resistance to antibiotics and it is imperative that all cases are treated with combinations of at least two drugs. The main drugs with antimycobacterial activity are rifampicin, ethambutol, pyrazinamide, clofazimine, sulfone, isoniazid, macrolide antibiotics, tetracyclines and quinolones. The management of all mycobacterial diseases must include not only the medical treatment but also a full range of educational initiatives aimed at the patient, the community and health personnel.

Diseases caused by rickettsiae

Rickettsiae are Gram-negative bacterial obligate intracellular parasites transmitted by blood-sucking arthropods. They are transmitted by ticks, mites, fleas and lice. The rickettsiae are released from the salivary glands of the tick or mite directly into the dermis, or in the case of flea or louse vectors, infected faeces are deposited on to the skin and rubbed into puncture wounds made by the organism. The rickettsiae may infect endothelial cells or macrophages, causing intravascular thrombosis and infarcts; increased capillary permeability results in extravascular fluid loss and sometimes frank vasculitis occurs in the skin, brain and heart. In the typhus group they spread from cell to cell by lysis of the infected cell. In the spotted fever group the infecting organisms spread rapidly using actin-based motility.

Diagnosis can be made by indirect immunofluorescence or enzyme-linked immunosorbent assay (ELISA)-based detection of IgG and IgM antibodies against type-specific rickettsial proteins. Treatment with antibiotics may rarely delay the rise in antibody titre. In addition, the organisms may be demonstrated in tissue samples by immunohistochemistry or direct immunofluorescence utilising monoclonal antibodies (Mab) against rickettsial proteins. The organisms may be cultured but are fastidious in their growth

requirements. PCR performed on tissue, blood or urine is now a sensitive and rapid tool where available to allow early diagnosis [59].

Spotted fever group

These are transmitted by ticks and include Rocky Mountain spotted fever, tick typhus and rickettsialpox.

Rocky Mountain spotted fever

Organism: *Rickettsia rickettsii*.

Vector: dog tick *Dermacentor varaiblis*; wood tick *D. andersoni*.

Reservoir: dogs.

Distribution: western hemisphere: Rocky mountains of North America, Maryland, Virginia, North Carolina, Mexico, Colombia, Brazil.

Clinical features The incubation period is between 3 and 12 days after the tick bite, but at least 40% of patients are unaware of the tick-bite episode. Young adult males are more commonly affected, with a seasonal peak in April to September in the US. Prodromal symptoms of headache, malaise and high fever (39–40°C) are followed 3–4 days later by a maculopapular rash on wrists and ankles. This spreads centrally to affect the trunk and face. Palms and soles are usually involved. The rash becomes haemorrhagic and may become confluent. Acral gangrene may occur, but 13% of patients may have no rash and in 20% it develops later in the illness. An eschar is generally not present. General examination may reveal hepatosplenomegaly, altered consciousness, renal failure and shock. Recovery usually occurs over 3 weeks with fatality rates of 1.5–6%. Mortality is higher in the elderly, those with coexisting disease and those with no known tick bite or rash.

Tick typhus

Clinical features The clinical features of the tick-borne typhus diseases (Table 12.3) are very similar and usually milder than those of Rocky Mountain spotted fever. Fatal cases are rare. The initial lesion develops at the site of the tick bite with an erythematous papule, which vesiculates and develops an overlying eschar, also called 'tache noir' (Figure 12.6) and local lymphadenopathy. Fever and headache develop and after about 5 days a widespread exanthem evolves, which usually involves the palms and soles. This is an erythematous maculopapular eruption but may become haemorrhagic.

Rickettsialpox

Organism: *R. akari*.

Vector: mites.

Reservoir: house mice, rodents.

Distribution: US, Russia, Africa.

Clinical features Rickettsialpox is a mild self-limiting disease. The initial skin lesion, which develops at the site of the mite bite after 7–10 days, is a 1–1.5 cm painless erythematous papule. Central vesiculation subsequently develops and becomes covered with a black eschar. This lesion heals slowly to leave a scar. Regional lymph nodes may be enlarged. Fever develops 3–7 days after the initial lesions and a widespread exanthem evolves. The rash has a widespread distribution and is maculopapular and vesicular in nature. Palms and soles are usually spared. The eruption heals without scarring.

Typhus group

Epidemic typhus

Organism: *R. prowazeki*

Vector: louse.

Reservoir: humans, flying squirrels.

Distribution: worldwide.

Epidemics are usually associated with displaced populations and refugees.

Clinical features The incubation time is 7–14 days. Prodromal symptoms consist of headache, fever and malaise, and

Table 12.3 Tick-borne typhus diseases

	Organism	Vector	Reservoir	Distribution
African tick typhus (boutonneuse fever/ Mediterranean spotted fever)	*Rickettsia conorii*	Ixodid tick	Rodents, dogs	Africa, Mediterranean
Siberian tick typhus	*R. sibirica*	Ixodid tick	Rodents	Russia, Central Asia
Queensland tick typhus	*R. australis*	Ixodid tick	Marsupials, rodents	Australia

after 4–7 days a rash develops in the majority of patients. Crops of erythematous macules appear on the trunk and spread centrifugally but spare the palms and soles. Conjunctival haemorrhage may be a feature. The skin lesions progress to purpuric lesions and gangrene of extremities may occur.

Sporadic typhus (Grill–Zinsser disease)

This is the recrudescence of epidemic typhus in individuals who have had an attack of the disease previously. It is usually milder and the skin features are not prominent.

Murine typhus

Organism: *R. mooseri*.
Vector: rat flea.
Reservoir: rodents.
Distribution: worldwide but increased in Central and South America.

Clinical features This is endemic to temperate and subtropical regions. Similar to epidemic typhus, but milder with less-marked cutaneous features. Only 50% of patients develop a rash. Recovery occurs within 2 weeks. Neither epidemic nor endemic typhus show an eschar at the site of infection.

Scrub typhus

Organism: *O. tsutsugamushi*.
Vector: mite.
Reservoir: rodents.
Distribution: indigenous to south and east Asia, northern Australasia and western Pacific.

Clinical features This is a severe infection which can cause pneumonia, myocarditis and meningoencephalitis, and has a mortality rate of 7% in untreated patients. An eschar may occur at the site of infection.

Management of rickettsial infections

This includes general supportive treatment and specific antirickettsial therapy. Empirical antibiotic therapy should be prescribed early if tick-transmitted rickettsioses are suspected, before confirmation of the diagnosis. The drugs of choice are doxycycline (100 mg PO/IV bd) and tetracycline (500 mg PO qds). Although tetracyclines are in all other circumstances contraindicated in children less than 9 years of age, these may also be the treatment of choice for children in potentially life-threatening illness [60–62]. Alternative treatments include chloramphenicol (50–75mg/kg/day) if this is the sole available drug, and the macrolides clarithromycin and azithromycin have also shown some efficacy in recent trials. Some fluoroquinolones may have efficacy against spotted fever rickettsiae, although these data are to date largely anecdotal. Many classes of broad-spectrum antibiotics, including penicillins, cephalosporins and aminoglycosides appear ineffective. The exact duration of antibiotic therapy is related to clinical response and should be continued for at least 3 days after the patient is afebrile to prevent recrudescence [63].

Diseases caused by fungi

Dermatophyte infections and malasseziosis

Superficial fungal infections by dermatophytes are cosmopolitan and affect any anatomical site, including scalp and nails; however, one of the commonest presentations in the traveller affects one or both feet. These fungi are transmitted to humans by direct skin contact from their habitat in the soil, vegetation or other individuals. Local conditions on the skin, such as a moist and hot environment while travelling, are predisposing factors. Dermatophyte infections are highly prevalent in tropical climates as this represents an ideal environment for these organisms: numerous case series and epidemiological studies from Latin America have been reported in the Spanish and Portuguese literature. The main genera involved in human infections are *Trychophyton*, *Epidermophyton* and *Microsporum*, but infections of the foot including the toenails, are caused particularly by *T. rubrum*. *T. mentagrophytes* and *E. floccosum*. Dermatophytes are keratinophylic organisms and exert their pathogenesis through attachment to the skin, nail or hair surfaces.

Individuals of both sexes and all age groups are affected by dermatophytes; however, children under the age of 10 rarely present with tinea pedis. The main clinical pictures are those of localised tinea pedis, interdigital, plantar hyperkeratotic and onychomycosis. Common names for these conditions include ringworm and athlete's foot. Dermatophyte infections can manifest as localised single or multiple circinate plaques with erythema and variable degrees of scaling on the body in cases of tinea corporis (Figure 12.15). Athlete's foot involves the dorsum or perimalleolar regions. Toe-web involvement is commonly bilateral, presenting with erythema, a burning sensation, pruritus and scaling, particularly of the fourth interdigital toe-web space. Severe acute forms present with painful erythema and blistering in a similar pattern to that found in cases of acute eczema or pompholyx. Patients with a history of atopy are predisposed to superficial infections by dermatophytes, and in these cases erythematous inflammatory fungal lesions coexist with

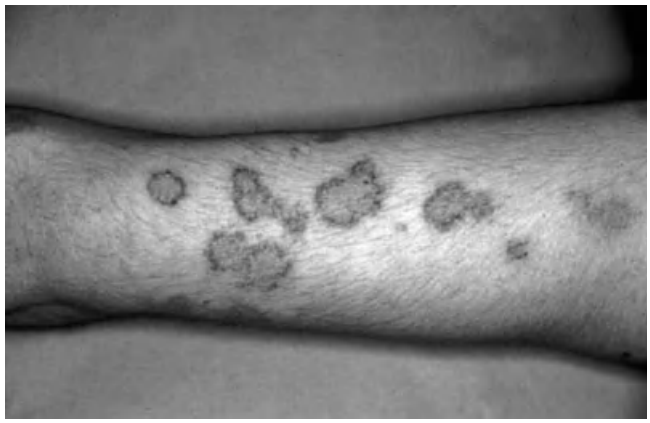

Figure 12.15 Tinea corporis from Southeast Asia. Discrete erythematous plaques with a circinate polycyclic border and pruritus.

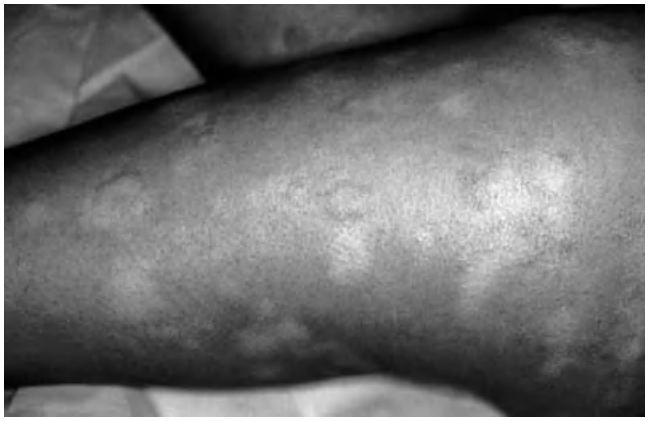

Figure 12.16 Tinea corporis in a traveller with atopic eczema. Erythematous polycyclic plaques from fungal infection and hypopigmented patches on eczematous skin.

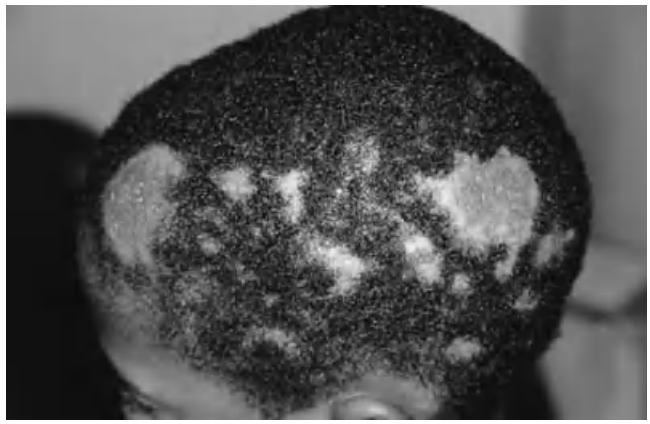

Figure 12.17 Kerion in a young traveller. Boggy inflammatory plaques on nonscarring alopecic patches of the scalp.

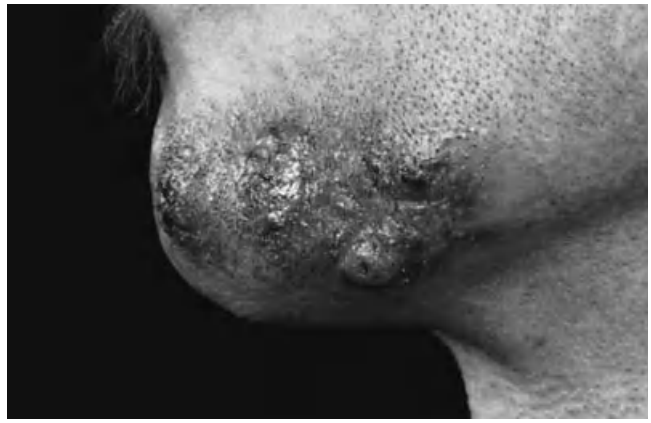

Figure 12.18 *Trychophyton mentayrophytes* granuloma of the chin from South America. Erythema and nodular lesions with areas of scarring.

patches of eczematous skin (Figure 12.16). Chronic plantar lesions develop asymptomatic large hyperkeratotic plaques and a particular form of toenail infection by *T. rubrum* manifests clinically as a subungual white onychomycosis. Varying degrees of temporary disability may result from severe infections. Children manifest scalp infections under the kerion clinical form with patches of non-scarring alopecia and boggy inflammation of the skin (Figure 12.17). Less commonly, adult travellers manifest granulomatous inflammation with varying degrees of scarring in infections caused by other species of *Trychophyton* (Figure 12.18).

Discrete plaques of granuloma annulare have to be considered in the differential diagnosis of localised ringworm, whereas thickened plaques of plantar psoriasis may pose diagnostic difficulties with chronic hyperkeratotic infections by dermatophytes. Other superficial skin and nail infections of the foot, such as those caused by *Candida* and *Scytalidium* species, may also present a diagnostic difficulty. The returning traveller from the tropics is often referred to the specialised clinic at HTD with severe or recurrent superficial yeast infections by *Malassezia furfur* (Figure 12.19).

The diagnosis of dermatophyte infection on the skin is made on clinical grounds. Additional diagnostic measures include direct microscopy of skin scrapings in 10–12% potassium hydroxide solution and the identification of the causative organism by culture in Sabouraud medium. A similar strategy is recommended for the laboratory diagnosis of pityriasis versicolor (malasseziosis), which requires special oily additives for successful isolation in culture.

The therapy of choice includes the use of topical and/or systemic azole or alylamine antifungal compounds. Localised infections require topical therapy for 3–4 weeks but cases with interdigital athlete's foot may require treatment for up to 6–8 weeks. Topical steroids are often required to

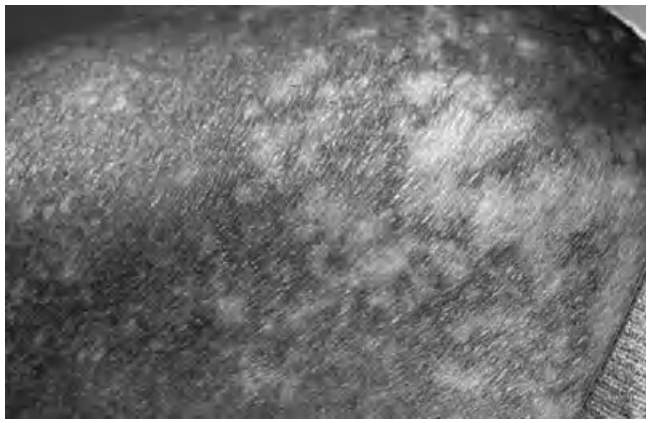

Figure 12.19 Malasseziosis of the trunk and upper limbs in a returning traveller. Small and coalescing hypopigmented asymptomatic patches.

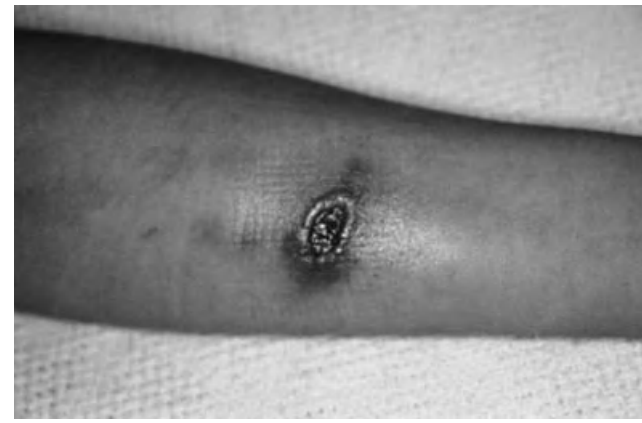

Figure 12.20 Sporotrichosis from Brazil. Forearm with erythematous nodular ulcer and lymphangitic track proximally. (Courtesy of Professor A.Bryceson)

control the inflammatory picture but are administered only when effective antifungal treatment is already in place. Systemic therapy with antifungals is indicated in severe skin infections and onychomycosis of the toenails. *M. furfur* infection responds to selenium sulphide preparations, ketoconazole shampooand other imidazolic or alylamine topical compounds applied for 6 weeks. Cases also respond to systemic triazoles. Other therapeutic measures address the control of symptoms, secondary eczematisation and superimposed bacterial infection. Measures of general hygiene and appropriate shoe wear are useful to prevent re-infection, which is a common problem in the traveller.

Sporotrichosis

Sporotrichosis is a subcutaneous or deep fungal infection acquired by direct inoculation of *Sporothrix schenckii* into the skin or subcutaneous tissue. Inhalation of infective organisms can also produce clinical disease; accidental exposure takes place outdoors as a result of an accidental or professional contact involving splinters, thorns, straw, wood shavings or other sharp objects. This dimorphic fungus is ubiquitous in nature and lives in the soil, bark of trees, shrubs and plant detritus. This is a worldwide disease of temperate humid and tropical areas and represents a risk for travellers. *S. schenckii* has a low pathogenic potential and causes disease by virulence factors that include extracellular enzymes and polysaccharides, as well as showing thermotolerance. The infective structures display a strong acid phosphatase activity and mannan compounds are capable of inhibiting phagocytosis by macrophages.

Sporotrichosis may manifest as a systemic illness in pulmonary forms but in most cases the disease is limited to the skin and subcutaneous and lymphatic tissues. The upper and lower limbs are the usual sites of inoculation. Following the traumatic episode the disease manifests as a localised skin nodule involving only the affected limb. This inoculation chancre develops a suppurative and granulomatous infection that remains fixed or else disseminates proximally via the lymphatic system (Figure 12.20). Satellite lesions may develop along the path of the lymphatic vessels (sporotrichoid spread). Superimposed bacterial infection may occur and verrucous lesions show a tendency to ulceration. The gold standard of laboratory diagnosis is the identification of the fungus in culture, but direct microscopy and histopathological investigations also have a diagnostic value. Outbreaks in parties of travellers require full epidemiological investigation.

Itraconazole 100–200 mg daily has become the drug of choice for both lymphocutaneous and fixed lesions of sporotrichosis [64, 65]. Fluconazole at a dose of 400 mg is less effective but is used as second-line treatment if the patient cannot tolerate itraconazole. Potassium iodide in increasing daily doses has been used since the early 1900s. It is inconvenient to take and has side effects; however, it is still recommended as it is effective and much less costly [66] than the alternatives. Amphotericin B is indicated for life-threatening or extensive pulmonary sporotrichosis [67]. As the disease is acquired by direct inoculation into the skin, preventive measures are of the utmost importance. Protective footwear, clothing and avoidance of skin contact with splinters, rough bark, plant detritus and soil are the most efficient methods of preventing the disease [68].

Systemic mycosis manifesting on the skin

Infections by *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis* commonly manifest with

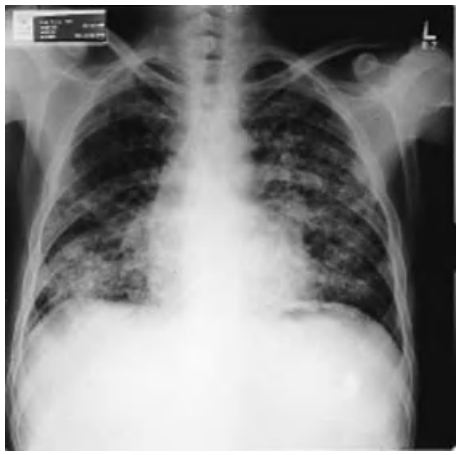

Figure 12.21 Paracoccidioidomycosis from Venezuela. Chest X-rays with bilateral nodular infiltrate of the lungs.

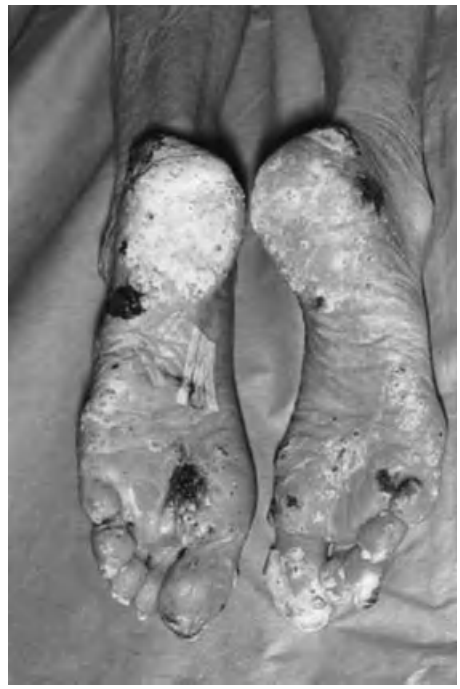

Figure 12.22 Paracoccidioidomycosis from Venezuela. Disseminated verrucous, hyperkeratotic and haemorrhagic ulcerated lesions on lower limbs.

disease of the lungs but haematogenous dissemination results in the appearance of skin lesions.

Coccidioidomycosis is acquired through inhalation of infective spores in tropical but also subtropical desert regions of the world, particularly in the American continent. Southern and western States in US and northwestern regions of Mexico are well-recognised endemic regions and the disease is acquired most commonly in urban areas. Travellers acquire the infection in urban areas where a high proportion of the resident population manifest a positive intradermal reaction on skin testing using coccidioidin. This systemic mycosis presents a risk particularly for the immunocompromised traveller. The skin becomes involved in a small proportion of cases and lesions manifest as erythematous, verrucous or scaling nodules on the face, upper limbs or on the plantar surface or any other part of the foot. A history of exposure in endemic regions followed by an episode of erythema nodosum supports the diagnostic possibility. Other investigations such as serology, chest X-rays and culture for the isolation of the organism confirm the diagnosis. Culture of agents causing systemic mycoses should only be carried out in specialised laboratories, as they represent a serious biological hazard. Systemic therapeutic options for coccidioidomycosis include amphotericin B and triazole compounds.

Paracoccidioidomycosis occurs in Mexico, Central and South America, predominantly affecting male individuals who live and acquire the infection in rural areas. Actual evidence of the mode of transmission is incomplete but the respiratory route seems to be common in acquisition of the infection. Following a chronic picture of lung involvement (Figure 12.21), weight loss and fatigue, the skin of one or both feet can be affected. Painful nodular, haemorrhagic, ulcerated and verrucous lesions can be observed, covered by a thick crust (Figure 12.22) and severe disability results in advanced forms of the disease. The diagnosis is based on the history of exposure in an endemic region (which may have occurred several years previously) [69] and the clinical picture, supported by investigations to reveal the presence of the typical large, budding yeast cells. These can be observed by direct microscopy and with H&E staining for histology and are easily identified in culture. Effective systemic treatment has been reported with triazole compounds and amphotericin B.

Patients with foot involvement from systemic fungal disease require immediate referral to an experienced hospital physician or specialists in mycology, infectious diseases, or dermatology.

Diseases caused by viruses

Most common viral skin diseases are cosmopolitan, but the onset may coincide with a trip to the tropics and pose problems in the differential diagnosis of the returning traveller. Viral infections that are prevalent in the tropics include *molluscum contagiosum* in children (Figure 12.23), plantar warts in adults, *Kaposi sarcoma* in patients with AIDS (Figure 12.24) and severe blistering forms of varicella. Severe cases

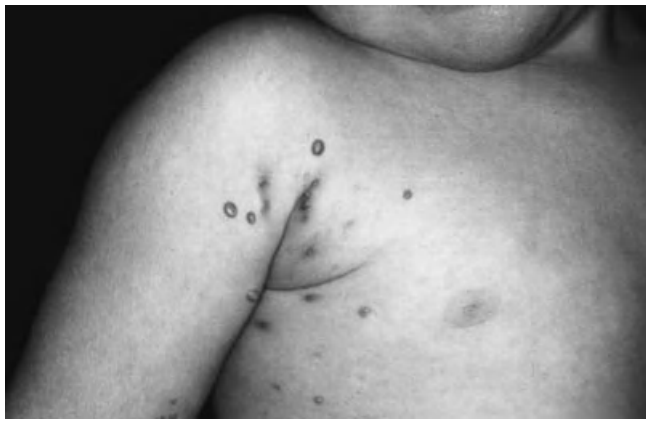

Figure 12.23 Molluscum contagiosum in a child. Umbilicated and erythematous/whitish millimetric papules on the trunk and upper limb.

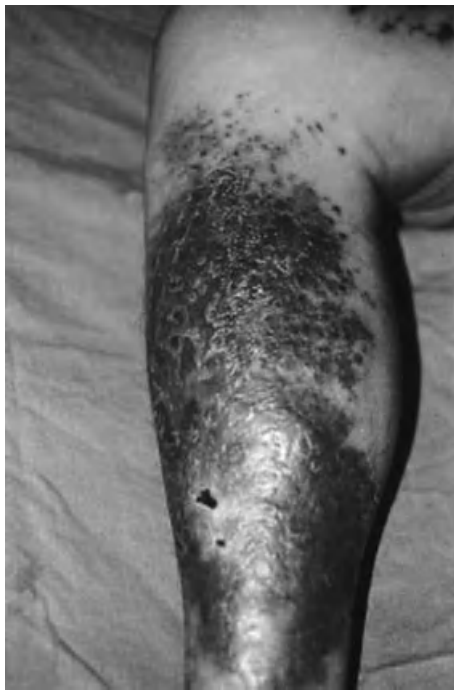

Figure 12.24 Kaposi sarcoma of the leg. Lymphangiomatous form in a traveller with AIDS.

require work-up following a full diagnostic protocol with specimens for culture, electron microscopy, serology and histopathology followed by specialised treatment in tertiary referral centres. Potentially severe arboviral infections causing exanthemata with fever such as dengue or chikungunya can also occur [70].

General dermatology related to travel

Skin disorders that may present to the travel medicine practitioner in addition to infections, include other dermatological conditions such as eczema, acne, psoriasis, urticaria, skin malignancies, photosensitivity disorders and a variety of other miscellaneous dermatological conditions. The differential diagnosis is based on the anatomical site affected and morphology of the lesions. The presentation of skin disorders may vary with the ethnic origin of the patient and may be affected by the travel environment.

Eczema

Eczema is one of the most common skin disorders arising from, or exacerbated by, a change in climate. Hot weather and sweating can make eczema worse and a cold, dry environment can also cause an exacerbation. Eczema, or dermatitis, refers to a family of pruritic conditions outlined below, the histological hallmark of which is epidermal oedema (spongiosis). The skin becomes inflamed, the skin barrier is disrupted and water is lost. Different types of eczema may coexist in the same patient [71].

Atopic eczema is associated with other atopic conditions such as asthma or hay fever. It is caused by both a defective barrier function of the skin and by altered immune responses to environmental allergens. IgE levels are raised. It presents as symmetrical, poorly defined, red, scaly lesions on flexural skin. Pruritus causes scratching, which further disrupts the skin barrier and can lead to colonisation with *Staphylococcus aureus*. Weeping of exudate and crusting are characteristic. Chronic lesions appear as lichenified plaques with excoriation, which results in accentuation of the normal skin lines.

Contact dermatitis exists in two forms – irritant and allergic. Irritant contact dermatitis results from contact with chemical compounds in the absence of an allergic mechanism and will occur in all individuals if the chemicals are applied in sufficient concentration. Allergic contact dermatitis is a type IV hypersensitivity allergic response, only occurring in certain individuals at even a very low level of exposure. Examples of this include allergies to metals, leather, hair dye, nail polish and some plants, for example ivy or mangoes. Patch testing can be useful in allergic contact dermatitis. From a practical point of view, the two types of contact dermatitis may be difficult to distinguish clinically [72].

Seborrhoeic dermatitis presents with a flaky, orangey-red eruption on the nasolabial folds and glabellar area, but can extend to the whole face, scalp and upper chest. It is a

very common scalp complaint. Overgrowth of the yeast Pityrosporum appears to cause an eczematous response. Management involves treating both the causative yeast with an antifungal and the eczematous response with topical steroids [73].

Pompholyx affects the acral skin of the palms or soles and is aggravated by sweating. Tiny pruritic vesicles occur and since the keratin layer of the palmoplantar skin is particularly thick, they do not burst or form crusts. Important differential diagnoses include contact dermatitis, palmoplantar psoriasis and scabies. Drug eruptions can also cause acral inflammatory eruptions. Treatment of pompholyx is with potent topical steroids.

Discoid eczema is a specific variant of eczema with symmetrical, well-defined, coin-shaped lesions. They tend to occur on the arms and legs and may or may not be pruritic. Important differential diagnoses include tinea, psoriasis or Bowen's disease. Tinea, however, tends to have a sharper border with a clearing centre, whereas discoid eczema is usually symmetrical and uniform throughout. Psoriasis usually presents with silvery scale rather than crust and Bowen's disease is normally solitary.

Follicular eczema is a type of atopic eczema in which only the hair follicles are involved. It is more common in darker skin and tends to present on the back, upper arms and thighs.

Photosensitive eczema is an eczematous eruption in exposed sites that is triggered by sunlight. This can occur in a small percentage of people, although in general, eczema improves with UV light in summer.

Treatment of eczema involves reducing the exposure to allergens, restoring the skin barrier and decreasing the patient's immune response. Soaps and detergents should be avoided and soap substitutes prescribed. Topical emollients should be applied liberally at frequent intervals. Emollient ointments are generally better than creams and do not contain preservative, which can cause an allergic reaction. Topical steroids can be used when emollients alone are unsuccessful. Patients may need to use different potencies at different sites, with higher strength topical steroids reserved for severe disease. In general, weaker steroids should be used on the face and flexures, with stronger steroids for more lichenified areas. Once symptoms have subsided, topical steroids should be slowly tapered. Topical immunomodulators such as tacrolimus, which lack the side effect of cutaneous atrophy associated with long-term topical steroids, can be particularly useful for eczema of the face in both adults and children [74]. Antihistamines are useful if lesions are excoriated. Coal tar preparations may be useful in resistant discoid eczema, or resistant plaques of lichenification [75]. Oral steroids may occasionally be needed in severe or resistant eczema.

Folliculitis

Folliculitis is a superficial inflammation of hair follicles. Although *Staphylococcus aureus* is the most common cause, many organisms can cause a folliculitis including Gram-negative bacteria, Pityrosporum yeast and herpes simplex. Folliculitis may also be non-infective due to occlusion from excessive application of greasy emollients or overuse of topical or oral steroids [76].

Folliculitis typically presents as 1 mm-wide monomorphic pustules, but can appear simply as erythematous papules without a pustule. The differential diagnosis of discrete papular lesions includes miliaria, insect bites, scabies, a drug rash or in middle-aged or elderly patients Grover's disease (discrete pruritic papules associated with increased sweating); however, these are all non-follicular.

Treatment is of the underlying infective agent or reducing or stopping application of greasy emollients or topical steroids. It is good practice to culture the pus by cleaning the skin, piercing the pustule with a sterile needle and swabbing the pustule contents. Persistent folliculitis may require an oral tetracycline for up to 6 months, or occasionally topical or oral retinoids.

Miliaria

Miliaria or prickly heat is caused by blocked eccrine sweat gland ducts. It is common in travellers visiting a hot humid climate and may develop within a few days of arrival. It appears as itchy non-follicular papules and vesicles, which may be erythematous or skin-coloured. It must be differentiated from folliculitis. Complications include secondary bacterial infection, pyoderma or a skin abscess. It is a self-limiting disorder treated by cool baths, cool clothing and fan or air-conditioned environments.

Acne

Acne is a common disease of the pilosebaceous unit involving four pathophysiological factors. Increased production of sebum occurs with blockage of the pilosebaceous duct, proliferation of the commensal bacterium *Propionibacterium acnes*, which breaks down the sebum into irritant fatty acids, and finally resultant inflammation. The underlying aetiology appears to be hormonally mediated via androgens. Tropical environments may increase sebum production and the traveller may develop either the first presentation or an exacerbation of acne.

Clinically this process results in the formation of either a comedone or an inflammatory lesion. Open comedones present as blackheads and closed comedones as whiteheads. The inflammatory lesions may present as papules, pustules

or cystic nodules. There is racial variation in morphology of acne, with those with black skin more likely to form comedones and those with white skin more prone towards inflammatory acne. Patients with black skin may respond to inflammatory acne by forming keloid scars. The distribution of acne occurs where the density of sebaceous glands is greatest, on the face, upper chest and upper back.

Treatment of mild acne is with topical agents. Topical retinoids are now used first line and may be co-prescribed with topical antibiotics. Adding topical benzoyl peroxide minimises antibiotic resistance [77]. Benzoyl peroxide may bleach hair and clothes and both topical retinoids and benzoyl peroxide can cause dryness of the skin. Topical azeleic acid can be useful if these are too irritant.

Treatment of moderately severe acne is with oral antibiotics. Oral tetracyclines are first line. Erythromycin can be used if tetracyclines are contraindicated or not tolerated. Trimethoprim (300 mg bd) is useful if erythromycin resistance is suspected. Oral antibiotics may be co-prescribed with topical retinoids. There is no evidence that combining oral and topical antibiotics is beneficial.

In severe or resistant acne oral roaccutane should be considered, as a 4- to 6-month course can achieve remission in more than 75% of cases. Retinoids should be used with extreme caution if the patient has a history of severe depression. Liver function and serum lipids must be monitored. Both topical and oral retinoids are contraindicated in pregnancy and women of childbearing age must use effective contraception during and for 2 months after completing oral retinoids. Both topical and oral retinoids can cause photosensitivity. Topical retinoids should therefore be applied at night and washed off in the morning and appropriate sunscreens should be used with oral retinoids [78].

Psoriasis

Psoriasis is a chronic autoimmune disease affecting the skin and joints. It has a genetic basis, but environmental factors are heavily implicated in first presentation and exacerbations. Some of these may be travel-related and include infection, trauma, medications (e.g. chloroquine), alcohol, smoking, HIV disease, sunlight and psychological stress. Although sunlight is usually beneficial in psoriasis, in a very small minority of patients it may provoke an exacerbation.

Psoriasis is a clinical diagnosis made by the presence of the characteristic skin lesions and nail changes. There are several clinical manifestations, below, which can develop simultaneously or sequentially over time in the same patient. A body surface area less than 5% indicates mild disease, 5–10% indicates moderate and more than 10% is considered severe.

Plaque psoriasis is the most common form, with symmetrical, well-defined, erythematous plaques with silvery scale. These are characteristically on extensor surfaces or the scalp. They may or may not be itchy. Plaque psoriasis is often accompanied by nail psoriasis.

Guttate psoriasis is characterised by numerous scaly droplet spots of psoriasis on the trunk, upper arms and thighs, and reflects an abnormal immune reaction to streptococcal throat infection. It usually affects children and in most cases is self-limiting. It can be confused with pityriasis rosea, although in the latter there is normally a 'herald patch' and these lesions are less scaly.

Flexural psoriasis occurs in the skin folds and genital area and typically presents with much less scale. Differential diagnoses to consider include fungal intertrigo or erythrasma.

Pustular psoriasis can occur in two forms, localised and generalised. Localised pustular psoriasis is relatively common and occurs on the palms and soles. Generalised pustular psoriasis is an unstable form of psoriasis in which extensive sheets of sterile yellow pustules appear on the skin, which may become painful and the patient may be systemically unwell.

Psoriasis can change from stable plaques to an unstable form such as erythroderma, which is a dermatological emergency in which >80% of the skin surface area becomes inflamed and erythematous. The patient is systemically unwell and may require admission. Other causes of erythroderma include eczema, seborrhoeic dermatitis, pityriasis rubra pilaris, cutaneous T cell lymphoma, underlying internal malignancy and drug reactions.

There is no cure for psoriasis and the aim of treatment is to control disease activity to a level that allows an acceptable quality of life with minimal drug toxicity. Treatments include topical therapy, phototherapy, systemic agents and the biological agents. Factors influencing the selection of treatment include the type of psoriasis, the extent of involvement, previous treatment and other medical disorders. Localised psoriasis can be managed with topical agents including emollients, vitamin D analogues, coal tar or dithranol. More generalised psoriasis may require assessment by a dermatologist and consideration for treatment with either phototherapy, methotrexate, ciclosporin, acitretin or combination treatment. The newer biological agents may prove a major advance in treatment in terms of less widespread immunosuppresion, but currently are indicated only for severe disease, owing to lack of data on long-term safety profile, long-term efficacy and cost [79].

Urticaria

Urticaria is a family of conditions characterised by red, raised, migratory itchy wheals. In black skin the erythema

may be less apparent. By definition an urticarial attack lasts less than 24 hours. Clinically it can be categorised as acute or chronic.

Acute urticaria is defined as occurring for less than 6 weeks. Medications, for example aspirin, are the commonest cause. Other common ingested allergens include nuts, fish, shellfish and eggs. When urticaria appears during spring and summer the role of inhaled allergens such as pollens and spores should be considered. The commonest acute contact urticarial reaction is to latex. Viral infections, or streptococcal pharyngitis in children, may cause a transient urticaria over weeks.

Chronic urticaria is defined as lasting more than 6 weeks. Chronic urticaria may be divided into the physical urticarias, angio-oedema, urticarial vasculitis and chronic idiopathic urticaria.

Physical urticarias may be caused by pressure, sweating, heat, cold, sunlight or water. They can be identified by the history and should always be considered, as this can avoid further extensive investigation. Delayed pressure urticaria can occur after 6–8 hours at sites of tight clothing or other prolonged pressure. Cholinergic urticaria can be induced by sweating, from exercise or hot environments. Cold urticaria may be tested for by placing an ice cube on the skin for 10 minutes and then observing a wheal appear 5–10 minutes later. Solar urticaria is very rare and occurs within minutes after exposure to sunlight. In aquagenic urticaria, which is also rare, wheals can develop within 30 minutes of exposure to water, irrespective of the temperature.

Angio-oedema is a form of urticaria in which the oedema is deeper in the dermis and subcutaneous tissues and the lesions last longer. Involvement of the upper airways may cause potentially fatal respiratory arrest. Recurrent angio-oedema may rarely be due to hereditary angioneurotic oedema in which there is a congenital defect in C1 esterase inhibitor.

Urticarial vasculitis is defined as urticarial lesions that persist for more than 24 hours. The lesions may be painful, may last several days and may be associated with angio-oedema. Urticarial vasculitis is a clinical finding and investigation for a cause of vasculitis should be undertaken, including histological investigation. The biopsy should include both lesional and non-lesional skin. It is most commonly associated with systemic lupus erythematosus (SLE).

Chronic idiopathic urticaria is a diagnosis of exclusion but comprises the commonest category in chronic urticaria. It can persist for years, apparently unrelated to any external allergen. Autoantibodies to mast cell receptors may occur in nearly half of these patients [80]. It may be associated with angio-oedema.

A comprehensive history and examination should always be undertaken. Extensive routine screening tests are unlikely to be helpful in acute urticaria [81]. In chronic urticaria, thyroid function, autoantibody profile, complement, ANCA, ACE, ENA and RAST tests may be considered as directed by the history. The differential diagnosis of urticaria or recurrent migratory swellings in the returning traveller includes helminth infections, and stool examination and serological investigation may also be indicated to exclude filariasis, schistosomiasis, strongyloides and gnathostomiasis.

Treatment is initially with a non-sedating antihistamine and if this does not help then a sedating antihistamine can be added at night. If the response remains poor, then an H2 antagonist such as cimetidine or a leukotriene receptor antagonist can also be added. Resistant forms of urticaria may require short courses of systemic steroids. Patients with severe angio-oedema may need adrenaline pens for emergency situations and those with hereditary angioneurotic oedema may also need treatment with infusion of C1 esterase inhibitor.

Skin malignancies

An important hazard of travel to locations in the world with higher risk of UV exposure are skin cancers. The various types of skin cancer may be characteristic from morphology alone, although histology is the gold standard for diagnosis. If one skin cancer is suspected or found, the patient should be examined for others.

Actinic keratoses

These are pre-malignant skin lesions that are common in patients with paler skin types at sites of maximal cumulative sun exposure. They present as poorly circumscribed, erythematous, scaly macules. They gradually enlarge and can vary in size from a several millimetres to a few centimetres. They may occasionally develop extensive scale. Actinic keratoses arising on the lip present as confluent scaliness with focal erosion, fissures and loss of definition of the vermilion border. The diagnosis is usually clinical; however, biopsy should be considered for lesions on the lip to exclude squamous cell carcinoma (SCC). Untreated actinic keratoses are associated with a small risk of transformation to SCC. A few isolated lesions can be treated with cryotherapy, or more widespread lesions can be treated with topical fluorouracil cream daily for 4 weeks. The patient should be warned to expect an intense inflammatory response with topical fluorouracil. If the lesions become too painful a moderately potent topical steroid may be substituted for a few days. A less irritant alternative is topical diclofenac gel for 3 months, which can have an efficacy as high as 50% and which rises the longer the cream is used [82].

Basal cell carcinoma

Basal cell carcinoma (BCC) is the most common cutaneous malignancy. BCCs may be slowly locally invasive, but rarely metastasise. They present most commonly on the head and neck and it is not uncommon for a patient to have more than one BCC at presentation. There are six clinical types of BCC, of which nodular BCC is the most common. These typically have a 'pearly' appearance, with well-defined, raised, rolled borders and telangiectasia. Morphoeic BCC is a rare but more aggressive type, which presents instead with the flat appearance of a scar and which in contrast has very poorly defined margins both clinically and histologically. The diagnosis of BCC is suspected clinically but confirmed on biopsy. Choice of treatment depends on the type, size and anatomical location. Treatment options include cryotherapy, topical immiquimod cream daily for 6–16 weeks, radiotherapy or excision. Moh's micrographic surgery, which involves layer by layer examination of excised tissue by the histopathologist concurrently while the patient is still in the operating theatre, has the highest cure rate and should be considered particularly for centrofacial lesions [83]. Although it may not be practical to follow up every isolated BCC, follow-up every 6 months for a few years should be considered to detect recurrence, as well as early identification of new lesions. High-risk sites for recurrence include the nose and ears.

Squamous cell carcinoma

Squamous cell carcinoma (SCC) is the second most frequent malignant skin tumour and has significant metastatic potential. Risk factors are cumulative UV exposure and immunosuppression after organ transplant. They may arise de novo, from actinic keratoses or from Bowen's disease (SCC in situ), and the classical presentation is with a hyperkeratotic, skin-coloured or erythematous papule, plaque or nodule. Typical sites are the head, neck and upper limbs. SCC may also arise from chronic oral or genital lichen planus, erythroplasia of Queyrat, genital lichen sclerosus, chronic periungual warts and from chronic scars, sinuses and leg ulcers. SCCs may grow slowly or rapidly and metastasise to the regional lymph nodes. Regional metastasis and local recurrence are dependent on location, size, depth, histological differentiation and treatment modality. Surgical excision is the treatment of choice, with adjuvant node dissection or radiotherapy in metastatic lesions. High-risk sites for metastasis and local recurrence include lesions on the ears and lip. The surgical treatment of SCC requires at least a 5 mm margin, with a wider margin or Moh's micrographic surgery for high-risk lesions including those >2 cm in diameter. Radiotherapy is an option for non-resectable tumours. Follow-up for at least 5 years is recommended.

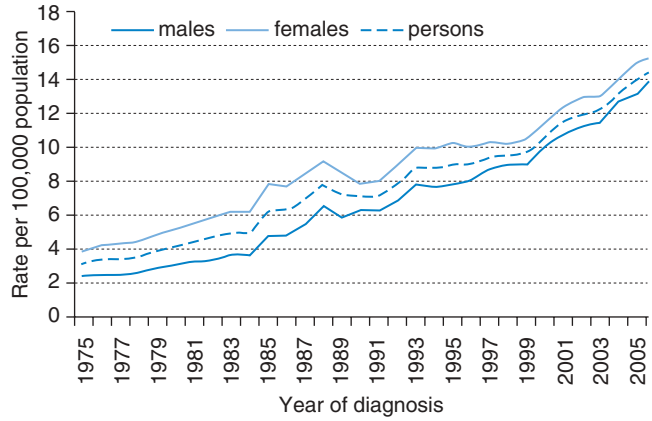

Figure 12.25 Age-standardised (European) incidence rates of melanoma, by sex, in Great Britain, 1975 to 2006.

Malignant melanoma

Malignant melanoma is a tumour of melanocytes. It is the most aggressive cutaneous cancer and metastasises early. Some studies suggest that the incidence in fair-skinned populations may be doubling every decade. Over the past 30 years in the UK, incidence has increased in males five times from 2.5 in 1975 to 14.3 in 2006, while in females rates haves tripled from 3.9 to 15.4 over the same period [84] (Figure 12.25).

Risk factors include paler skin type, sunburn in childhood, the atypical mole syndrome, large congenital melanocytic naevi and family history. Melanoma typically presents as a new or changing pigmented macule or nodule. The spread of a melanoma involves two growth phases – radial growth and vertical growth. Radial growth produces a flat, pigmented macule that spreads laterally along the skin surface in two dimensions. At some point the vertical growth phase is then entered and the melanoma can grow both upwards and downwards, producing a pigmented nodule.

The main clinical variants of melanoma are:

- superficial spreading – most common form; a macule in the horizontal growth phase
- nodular – appears as a pigmented nodule already in vertical growth phase
- lentigo maligna melanoma – arises in a pre-existing lentigo maligna
- acral lentiginous – most common form in darker skin; on palms, soles or nail bed
- amelanotic melanoma – non-pigmented nodule; may be confused with pyogenic granuloma.

The following standard ABCDE classification may help to identify a suspected melanoma:

- A – Asymmetry of shape
- B – Border irregularity
- C – Colour irregularity

Table 12.4 Disorders caused by exposure to ultraviolet irradiation

Acute photosensitivity	Chronic photosensitivity
Sunburn	Photoageing
Phototoxicity	
Plant-induced	
Drug-induced	
Photoallergy	
Solar urticaria	
Drug-induced	
Idiopathic	
Polymorphic light eruption	
Systemic lupus erythematosus	Skin malignancy

- D – Diameter > 7 mm
- E – Enlargement/Elevation

Prognosis is dependent on the Breslow thickness, which is the distance in millimetres from the stratum granulosum to the deepest cancerous cell. Mortality drops with increasing Breslow thickness, with an almost linear relationship. Tumours with a Breslow thickness <0.5 mm almost never metastasise and tumours <0.75 mm have a 95% 5-year survival rate. Tumours >3 mm, however, are associated with only a 50% 5-year survival. Sentinel lymph node biopsy aids tumour staging. Extracutaneous disease is essentially incurable. The definitive treatment for melanoma is excision. Suspicious pigmented lesions should be excised by a specialist without delay, by a narrow 2 mm margin, with a subsequent re-excision margin dependent on the Breslow thickness [85].

Photosensitivity disorders

Topical agents, oral medications and a wide variety of cutaneous and systemic diseases may all be associated with photosensitivity. Photosensitivity is recognised by the typical distribution of lesions – on the face, base of neck, upper chest, forearms, the back of the hands and lower legs. The eyelids, under the chin and behind the ears are usually spared. Specific attention should be paid to the following points in the history – age of onset, gender, timing of the eruption in relation to sun exposure, whether the eruption is seasonal, burning rather than itch (more common with drug-induced phototoxic reactions or certain porphyrias), oral medications, topical agents including sunscreens and any family history of autoimmune disorders, genetic disorders, or porphyria.

Sunburn

Sunburn is an acute inflammatory reaction of the skin due to excessive exposure to UV light. It presents with erythema and tenderness. When severe it can cause blistering, oedema and systemic symptoms. The diagnosis is made following clinical examination. Treatment comprises soothing agents such as calamine lotion and cool compresses, and if severe, analgesics, bed rest, topical or systemic steroids and fluid replacement.

Solar urticaria

This is a rare disorder in which UVA, UVB and visible light may produce itchy wheals after a few minutes' exposure. A tingling sensation and erythema precede the development of whitish wheals or urticaria which fades within a few hours. It can occur through glass. It is more common in females, who become affected between 10 and 50 years of age. It may rarely be associated with lupus erythematosus. The differential diagnosis may include polymorphic light eruption (PLE), or cholinergic urticaria due to sweating and an accurate history of timing of onset must be obtained. In young children it may be necessary to exclude erythropoetic porphyria. Treatment involves sun avoidance, sunscreens, antihistamines and phototherapy in selected patients [86].

Polymorphic light eruption

Polymorphic light eruption (PLE) is a common condition that normally occurs in spring, although onset may be in winter if travelling from northern latitudes to the tropics. It is more common in women, usually in the second decade, although it can occur in childhood. It is common in all races and skin types. It occurs up to 24 hours after UV exposure of several hours and can last up to 2 weeks. It may be provoked by UVA and therefore may occur through glass. It presents with either papules, vesicles, nodules, plaques, purpura or target-like lesions, and one type of lesion tends to predominate and recur in each patient. It often spares the face, as this is habitually exposed. The diagnosis is usually clinical. The differential diagnosis includes systemic lupus erythematosus (SLE) and serology must therefore be checked. Biopsy may be necessary in complex cases with urticated plaques or purpura. Prevention is important with photoprotection. UVB phototherapy may help at the onset of spring to induce tolerance. Oral steroids may be used for severe flares. Prednisolone 20 mg/day may suppress the eruption for the duration of a 2-week holiday. Alternatively hydroxychloroquine 200 mg bd may provide partial protection for 1 week prior to and during travel [87].

Rosacea

Rosacea is more common in those with paler skin types, although the cause is unknown. Environmental factors

exacerbate rosacea and many may be related to travel. These include alcohol, spicy food, a warm environment, including excessively hot or long showers, saunas, sunlight and increased emotion.

It presents with erythema, papules and pustules on the central face, typically the nose, cheeks, central forehead and point of the chin. Telangiectasias may accumulate over time, which are not a feature in acne. Also unlike in acne, comedones are absent. Significant facial oedema can sometimes occur. Ocular rosacea is an important association, with blepharitis, conjunctivitis or keratitis. Ocular involvement can rarely be sight-threatening and if it does not respond quickly to oral tetracyclines an expert opthalmological opinion should be sought.

The common differential diagnoses of a red face include acne, seborrhoeic dermatitis, atopic eczema, contact eczema, erysipelas, SLE or drug-induced photosensitivity. Acne generally occurs at a younger age and comedones may be present. Sebhorrhoeic dermatitis is scaly, with no pustules and the nasolabial folds are affected rather than the cheeks. In SLE there are no papules or pustules and the patient may be systemically unwell.

Rosacea is a chronic condition and management aims for control rather than cure. Treatment of mild rosacea includes the administration of topical metronidazole gel twice daily, or topical azeleic acid. Oral tetracyclines for 3–6 months are the mainstay of treatment of severe rosacea. Both topical and oral agents are unlikely to affect fixed erythema or telangiectasia, although these may respond to laser treatment. All topical steroids must be avoided as they can precipitate or exacerbate rosacea and patients should be warned that this may initially flare on stopping the topical steroids.

Sun avoidance is vital in management of rosacea and patients should use sunscreens regularly during the summer months, even on cloudy days, as UV light will contribute to telangiectasia and fixed irreversible erythema. People with rosacea may be sensitive to many creams or oils and sunscreens should be tested on a small area initially [88].

Lupus erythematosus

Cutaneous lupus includes systemic lupus erythematosus (SLE), subacute lupus and discoid lupus erythematosus (DLE). All types may be aggravated by sunlight.

SLE may present solely with cutaneous manifestations. These include the butterfly facial rash, urticaria lasting longer than 24 hours and often leaving bruising, a vasculitic rash or rarely blisters. Systemic features may include arthritis, pleuritis, pericarditis, proteinuria or neurological manifestations. Diagnosis can be made by serology, biopsy and four out of 11 symptom criteria, which do not have to be simultaneous. Antinuclear antibody is often positive and is useful as a screening test, but has varying degrees of sensitivity and specificity. Autoantibodies may show a speckled pattern and ENA (extractable nuclear antigens) may be positive, as well as other antibodies such as DNA antibodies and smooth muscle antibodies. Complement levels should be tested in patients with active lupus, as low levels may be linked with renal involvement. Important cutaneous differential diagnoses include PLE, rosacea and drug-induced photosensitivity. A wide range of drugs may provoke a lupus-like eruption and in some cases patients may have a positive ANA, but anti-double stranded DNA antibodies and hypocomplementaemia are rare in drug-induced lupus [89]. Treatment may involve oral steroids or hydroxychloroquine.

Subacute lupus presents with burning, annular plaques in sun-exposed areas. It has a similar timing of onset to PLE, but lasts longer – up to weeks or months. It may spare the face and does not scar. A common feature is a negative ANA test but positive anti-Ro antibody. Treatment may involve topical steroids or the antimalarials chloroquine or hydroxychloroquine. Hydroxychloroquine is used more commonly, as it is less likely to cause irreversible retinal damage. Subacute lupus appears to have a good prognosis over time [90].

Discoid lupus is the most common form of lupus. It starts as red, scaly plaques, which progress to form a triad of photosensitivity, atrophy and scarring. It usually affects the face or scalp, including the ears and tip of the nose. It may cause both hypo- and hyperpigmentation. It can cause a scarring alopecia. Differential diagnoses to consider include sarcoidosis and, in those who have been living in endemic areas, cutaneous TB. Diagnosis is by serology and biopsy. There is usually no systemic involvement, but it may coexist with SLE, or progress to SLE (particularly in those with extensive lesions), and ANA titres should be monitored regularly. Around 20–30% of patients with discoid lupus erythematosus (DLE) have a positive ANA, but fewer than 10% progress to SLE. To treat DLE a potent topical steroid may be used on the face as the risks of scarring from untreated DLE are very high. An oral antimalarial is used in extensive or resistant lesions. Sun protection is important. The risk of future SCC may be increased in chronic lesions of DLE.

Dermatomyositis

Dermatomyositis is a photosensitive eruption associated with proximal muscle weakness. The skin changes may precede the myositis. The rash consists of purplish patches or plaques, often including the eyelids. There may be considerable oedema on the face and arms. Splinter haemorrhages may occur with nailfold telangiectasia and purplish plaques on the knuckles called Gottron's papules. The differential diagnosis includes SLE, there is an association with

SLE and anti-nuclear antibodies (ANA) may be positive in up to 50% of patients. The diagnosis can be confirmed by a raised CK, EMG and muscle biopsy. Initial treatment is with high dose steroids and immunosuppressive agents may be required. In patients over the age of 40 there may be an associated internal malignancy [91].

Porphyria cutanea tarda

This is the most common type of porphyria and is due to reduced levels of uroporphyrinogen decarboxylase in the liver. A small number of cases are hereditary, but most are sporadic, with associated factors including excess alcohol, exogenous oestrogens, subclinical haemochromatosis, iron, antimalarials (high doses) and hepatitis C infection. There is usually some delay between sun exposure and the development of lesions and patients may appear sun-tanned. It presents primarily with skin fragility, causing vesicles and erosions on the dorsum of hands, forearms, face and bald scalp. Milia may be present. There may be atrophic scars from previous healed lesions. Mottled hypo- and hyperpigmentation can occur. Patients may develop hypertrichosis on the face. Differential diagnoses to consider include dermatitis, scabies and other blistering diseases; however, the latter should not normally be restricted to sun-exposed sites. The diagnosis is made from elevated urinary porphyrins. Liver enzymes and ferritin should be checked, including markers for hepatitis C infection if at risk. Treatment includes sun avoidance (even through glass), alcohol reduction, discontinuing precipitating drugs and venesection (500 ml fortnightly until ferritin normal or symptoms abate) with low-dose chloroquine or hydroxychloroquine twice weekly [92].

Chronic actinic dermatitis

This is a persistent eczema in sun-exposed sites, usually in those over the age of 60 who have been exposed to the sun over many years. There is a strong male predominance. The problem is initially apparent in summer, but the duration of symptoms gradually extends into winter months and eventually becomes perennial. An eczematous rash with severe itch affects the sun-exposed areas of the body and can gradually spread to covered sites. Minor sunlight exposure, even through glass, may then provoke symptoms. The differential diagnosis includes eczema and drug-induced photoallergy. Confirmation of the diagnosis is by phototesting, but patch testing is also indicated. This often reveals multiple contact allergens and there is a high frequency of allergy to sunscreens. Chronic actinic dermatitis forms a spectrum of disease that may progress to a more infiltrated skin eruption that may be difficult to distinguish from cutaneous lymphoma. Treatment includes avoidance of sunlight and allergens, emollients, topical steroids and in some cases oral steroids or immunosuppressive agents.

Lichen planus

Lichen planus is a moderately common skin disorder, thought to be due to a localised abnormal immune reaction to the skin, provoked by either a viral infection, trauma, or drugs. It exhibits koebnerisation and can occur at sites of even minor trauma. It presents with intensely pruritic, violaceous, polygonal papules. In those with darker skin, lesions may appear brown or black rather than violaceous. White lacy streaks known as Wickham's striae may be apparent on the surface, or in the buccal mucosa. Common sites of presentation are the wrists, ankles, genital area and scalp, where it may cause a scarring alopecia. It can present in a variety of patterns, including linear, annular, follicular, guttate, bullous, hypertrophic and actinic. Actinic lichen planus may cause annular brown plaques in sun-exposed sites in children or young adults often of Middle Eastern origin and may be confused with melasma. In the majority of cases lichen planus clears spontaneously within 18 months, but can persist longer in the mouth or genitals. Biopsy may be required particularly if asymmetrical, or if mucosal leucoplakia is present. Treatment of the pruritus is with a potent topical steroid. Patients with extensive disease or severe mucous membrane lichen planus may require oral steroids, oral hydroxychloroquine or phototherapy (except in actinic lichen planus). Postinflammatory hyperpigmentation can be persistent in darker-skinned patients. Chronic erosive oral or genital lichen planus carries a small risk of transformation to SCC [93].

Phytophotodermatitis

Phytophotodermatitis is inflammation caused by contact with certain plants just prior to, or during, exposure to UV light. This occurs more commonly in hot climates. It is due to photosensitising chemicals called psoralens present in several plant families, such as lime, lemon, giant hogweed, celery, parsnip, carrot, dill, parsley and fig. A common cause is splashes of lime juice on the skin from cold drinks. It may also be caused by perfumes or aromatherapy based on bergamot oil. It manifests usually as either urticaria or as eczema with vesicles and bullae, usually in a bizarre pattern consistent with the exposure to the plant or plant extract. Treatment is with antihistamines, antiseptics and wet dressings for any vesicular lesions or topical steroids. Residual pigmentation can be a characteristic feature and sunscreens are then important.

Drug-induced photosensitivity

A wide variety of drugs can cause photosensitivity. The commonest mechanism is phototoxicity that is not immunologically mediated. However, some drugs can cause immunologically mediated photoallergy, in which UV light converts the drug into an allergen. The two types can coexist.

Phototoxicity is an exaggerated sunburn response in patients who have not been exposed excessively. It can occur in all skin types. It occurs within 24 hours of exposure and often improves within 1–2 weeks of withdrawing the causative drug. These reactions usually produce a burning sensation, rather than itch. Many drugs may be responsible including amiodarone (up to 30–50% of patients), the antimalarials chloroquine or hydroxychloroquine, phenothiazines, tricyclics, tetracyclines, sulphonamides, NSAIDS, the oral contraceptive pill, frusemide and thiazides. Pigmentation may be a feature.

Photoallergy presents with a more eczematous rash, which can spread to non-exposed skin. There may be a latent period of several weeks between exposure and onset and the rash may be prolonged even after withdrawal of the causative agent. Drugs that can cause photoallergy include antimalarials, phenothiazines and sulphonamides. Topically applied photosensitisers are also a common cause, for example from aftershaves or sunscreens. Patients with milder photoallergy may have been on the drug for many summer months before symptoms develop, but those with severe photoallergy can develop a rash regardless of the season.

The differential diagnosis includes simple sunburn, atopic eczema, contact eczema, photosensitive eczema or other photosensitivity disorders. Investigations include phototests and photopatch tests. Treatment includes withdrawal of the drug and use of sunscreens until symptoms abate. Oral antihistamines or topical steroids may be required [94].

Skin disorders due to antimalarial drugs

As well as causing photosensitivity, antimalarials taken for long periods by the traveller may be associated with other cutaneous reactions. Chloroquine and hydroxychloroquine can cause pigmentation in up to 25% of patients after 4 months. These may be blackish-purple patches on the shins, or brown-grey pigmentation on sun-exposed sites, and the nails may also be affected. Chloroquine and hydroxychloroquine can also cause lichenoid reactions, with or without oral lesions. The antimalarials chloroquine or hydroxychloroquine may precipitate psoriasis or porphyria cutanea tarda.

Fixed drug eruption

This is a particular reaction whereby each time a certain drug is given a rash will re-occur at the same localised site. It presents within 24 hours, usually as a well-demarcated red plaque a few centimetres in diameter with or without blistering. Distal limbs or the glans penis are typical sites. Lesions are usually solitary, but may increase in number with repeated exposure. After discontinuation of the causative drug, the plaque slowly disappears over around 10 days leaving hyperpigmentation persisting for several months. Common causative drugs include sulphonamides, tetracyclines, quinine and non-steroidal anti-inflammatory drugs (NSAIDs). The differential diagnosis of any rash always recurring at the same site includes herpes simplex and contact dermatitis.

Melasma

Melasma is a common, acquired, benign, symmetrical form of facial hyperpigmentation found primarily in adult women. It may arise due to sunlight exposure, pregnancy or the combined oral contraceptive pill. It commonly affects the cheeks, forehead and upper lip. It may appear as large, well-circumscribed, pale brown patches, or as scattered confetti-like pale brown macules. Combined oral contraceptives should be avoided and sun protection is important. The pigmentation is epidermal and should fade slowly with time. It may respond to topical therapy such as topical 2% hydroquinone or Kligman's solution, although the former can cause variable dyspigmentation and the latter is irritant and requires slowly increasing application time.

Post-inflammatory hyperpigmentation

Post-inflammatory hyperpigmentation is a common response of the skin to injury. A hyperpigmented patch at the site of a prior inflammatory condition is typical. It may be caused by scratching or rubbing an itchy dermatosis such as eczema or lichen planus, may occur after drug-induced eruptions or exposure to any irritating topical chemical. Any part of the body may be affected. The hyperpigmentation may be epidermal or dermal. Epidermal hyperpigmentation tends to be lighter brown and well circumscribed, may be amenable to topical treatments and can fade within 6–12 months. Dermal hyperpigmentation tends to be darker and poorly circumscribed, is not amenable to topical treatments and can take years to fade as the pigment is very slowly phagocytosed by macrophages. The primary goal of therapy is prevention of further inflammation and trauma by treatment of the underlying inflammatory condition and daily use of a sunscreen, as sun exposure aggravates the pigmentation.

Post-inflammatory hypopigmentation

Just as some individuals develop hyperpigmentation in response to injury, partial loss of pigment can occur in other

individuals following the same inflammatory stimulus. This is distinguished from vitiligo by being poorly circumscribed and only partially hypopigmented rather than fully depigmented. It is less well defined than pityriasis versicolor and produces little or no scale on scratching the surface of the epidermis. Important differential diagnoses also include leprosy and sarcoidosis. Treatment involves that of the underlying skin condition and reassurance that the skin colour will slowly return with sunlight exposure over several months.

Vitiligo

Vitiligo is an autoimmune disease that causes symmetrical, sharply demarcated patches of complete depigmentation on the skin. There may be a positive family history in up to 30% of patients and it may be associated with other autoimmune diseases such as autoimmune thyroid disease, pernicious anaemia, diabetes and Addison's disease. The depigmented patches may slowly progress and may be significantly disfiguring. Potent topical steroids, topical tacrolimus 0.1% bd for up to 3 months, or phototherapy may be tried, but treatment success can be variable. Camouflage creams can be prescribed. Sun protection is very important for the patient travelling to sunny areas as there is a significant risk of burning.

Chilblains (Perniosis)

This is a common abnormal vascular reaction that can develop in cold environments. It presents as painful, throbbing, red or purple patches on the digits, over other bony areas, or over areas of fatty tissue. They typically feel cold to the touch, but the white vasospasm of Raynaud's phenomenon is not a feature. The lesions may last with itch for several weeks. They can occasionally develop blisters or necrosis. If recurrent the differential diagnosis includes chilblain lupus erythematosus [95].

Conclusion

Skin conditions are common in the returning traveller. These may comprise common pyogenic infections, tropical infections or non-infective skin conditions. Diagnosis must take into account the geographical area visited, body anatomical site affected and morphology of the skin lesions. It should be borne in mind that the presentation of common skin disorders may vary with the ethnic origin of the patient, and also due to the change in travel environment. It is also important to remember that the skin condition may be a primary condition or may represent a secondary manifestation of systemic disease.

References

1. Blackwell V and Vega-López F (2000) Two years of cutaneous larva migrans in London. *Br J Dermatol* **143**(Suppl. 57): 53–54.
2. Caumes E *et al.* (2002) Cutaneous larva migrans with folliculitis: report of seven cases and review of the literature. *Br J Dermatol* **146**: 314–316.
3. Caumes E (2003) Treatment of cutaneous larva migrans and Toxocara infection. *Fund Clin Pharm* **17**: 213–216.
4. Hochedez P and Caumes E (2008) Common skin infections in travelers. *J Travel Med* **15**(4): 252–262.
5. WHO (1990) Control of leishmaniasis: report of a WHO expert committee. *World Health Organization Technical Report Series* **793**.
6. Mendoza-León A *et al.* (1996) A guide for the cutaneous leishmaniasis connoisseur. In: Tapia F., Cáceres G. and Sánchez M. (eds) *Molecular and Immune Mechanisms in the Pathogenesis of Cutaneous Leishmaniasis*, pp. 1–21, 25–47. Springer, Heidelberg.
7. Scarisbrick JJ *et al.* (2006) Clinical features and diagnosis of 42 travellers with cutaneous leishmaniasis. *Travel Med Infect Dis* **4**: 14–21.
8. Faber WR *et al.* (2003) Value of diagnostic techniques for cutaneous leishmaniasis. *J Am Acad Dermatol* **49**: 70–74.
9. Palumbo E (2009) Current treatment for cutaneous leishmaniasis: a review. *Am J Ther* **16**: 178–182.
10. Lupi O *et al.* (2009) Tropical dermatology: tropical diseases caused by protozoa. *J Am Acad Dermatol* **60**: 897–925.
11. Stingl P (2009) Onchocerciasis: developments in diagnosis, treatment and control. *Int J Dermatol* **48**: 393–396.
12. Gardon J *et al.* (2002) Effects of standard and high doses of ivermectin on adult worms of Onchocerca volvulus: a randomised controlled trial. *Lancet* **360**(9328): 187–195.
13. Whitworth JA *et al.* (1996) Clinical and parasitological responses after up to 6.5 years of ivermectin treatment for onchocerciasis. *Trop Med Int Health* **1**(6): 786–793.
14. Hoerauf A *et al.* (2009) Efficacy of 5-week doxycycline treatment on adult Onchocerca volvulus. *Parasitol Res* **104**(2): 437–447.
15. Taniguchi Yando K and Isoda K (1992) Human gnathostomiasis: successful removal of *Gnathostoma hispidum*. *Int J Dermatol* **31**: 175–177.
16. Kraivichian P *et al.* (1992) Albendazole for the treatment of human gnathostomiasis. *Trans R Soc Trop Med Hyg* **86**: 418–421.
17. Nontasut P *et al.* (2000) Comparison of ivermectin and albendazole treatment for gnathostomiasis. *SE Asian J Trop Med Public Health* **31**: 374–377.
18. Herman JS and Chiodini PL (2009) Gnathostomiasis, another emerging imported disease. *Clin Microbiol Rev* **22**(3): 484–492.
19. Franco-Paredes C (2008) Filariasis caused by Loa Loa is also a cause of angioedema. *Am J Med* **121**(10): e29.
20. Rakita RM *et al.* (1993) Loa Loa infection as a cause of migratory angioedema: report of three cases from the Texas Medical Center. *Clin Infect Dis* **17**: 691–694.

21. Boussinesq M (2006) Loiasis. *Ann Trop Med Parasitol* **100**(8): 715–731.
22. Tyring SK *et al.* (2006) *Tropical Dermatology*. Elsevier Churchill Livingstone, Philadelphia.
23. Ibanez-Bernal S and Velasco-Castrejón O (1996) New records of human tungiasis in Mexico (Siphonaptera: Tungidae). *J Med Entomol* **33**: 988–999.
24. Douglas-Jones AG *et al.* (1995) Cutaneous infection with *Tunga penetrans*. *Br J Dermatol* **133**: 125–127.
25. Veraldi S and Valsecchi M (2007) Imported Tungiasis: a report of 19 cases and review of the literature. *Int J Dermatol* **46**: 1061–1066.
26. Heukelbach J and Feldmeier H (2004) Ectoparasites – the underestimated realm. *Lancet* **363**: 889–891.
27. Lui H and Buck W (1992) Cutaneous myasis: a simple and effective technique for extraction of *Dermatobia hominis* larvae. *Int J Dermatol* **31**: 657–659.
28. Currie BJ *et al.* (2004) First documentation of in vivo and in vitro ivermectin resistance in *Sarcoptes scabiei*. *Clin Infect Dis* **39**: e8–12.
29. Hicks MI and Elston DM (2009) Scabies. *Dermatol Ther* **22**(4): 279–292.
30. Dana AN (2009) Diagnosis and treatment of tick infestation and tick-borne diseases with cutaneous manifestations. *Dermatol Ther* **22**: 293–326.
31. Cherilyn S *et al.* (2008) *Bartonella* spp and *Rickettsia felis* in fleas, Democratic Republic of Congo. *Emerg Infect Dis* **14**(12): 1972–1974.
32. Fournier PE *et al.* (2002) Human pathogens in body and head lice. *Emerg Infect Dis* **8**(12): 1515–1518.
33. Steen CJ *et al.* (2004) Arthropods in dermatology. *J Am Acad Dermatol* **50**(6): 819–842.
34. Goddard J and deShazo R (2009) Bed bugs (*Cimex letularius*) and clinical consequences of their bites. *JAMA: J Am Med Assoc* **301**(13): 1358–1366.
35. Tankersley MS (2008) The stinging impact of the imported fire ant. *Curr Opin Allergy Clin Immunol* **8**(4): 354–359.
36. Norton SA and Lyons C (2002) Blister beetles and the ten plagues. *Lancet* **359**(9321): 1950.
37. Diaz JH (2009) Epidemiology, diagnosis, managementand prevention of common caterpillar envenomations in world travellers. *J Br Travel Health Assoc* **XIII**: 38–46.
38. Hossler EW (2009) Caterpillars and moths. *Dermatol Ther* **22**(4): 353–366.
39. Stuiver PC (1984) Acute schistosomiasis (Katayama Fever). *Br Med J* **288**: 221–222.
40. Haddad V Jr *et al.* (2009) Tropical dermatology: marine and aquatic dermatology. *J Am Acad Dermatol* **61**(5): 733–750.
41. Bisno AL and Stevens DL (1996) Streptococcal infections of skin and soft tissues. *New Engl J Med* **334**: 240.
42. Elliot DC *et al.* (1996) Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. *Ann Surg* **224**: 672–683.
43. Lee V and Kinghorn G (2008) Syphilis: an update. *Clin Med* **8**(3): 330–333.
44. Lautenschlager S (2006) Cutaneous manifestations of syphilis: recognition and management. *Am J Clin Dermatol* **7**(5): 291–304.
45. Karp G *et al.* (2009) Syphilis and HIV co-infection. *Eur J Intern Med* **20**(1): 9–13.
46. WHO (1986) Expert committee on venereal diseases and treponematoses: sixth report. *World Health Organization Technical Report Series* **736**.
47. WHO (2003) Review of current evidence and comparison of guidelines for effective syphilis treatment in Europe. *World Health Organisation*.
48. Sehgal VN *et al.* (1994) Yaws control and eradication. *Int J Dermatol* **33**: 16–20.
49. Castro LG (1994) Nonvenereal treponematosis. *J Am Acad Dermatol* **31**: 1075–1076.
50. Walker SL and Hay RJ (2000) Yaws: a review of the last 50 years. *Int J Dermatol* **39**: 258–260.
51. Weber MA *et al.* (2005) Magnetic resonance imaging of tropical ulcers. *Eur Radiol* **15**: 2375–2376.
52. Ngu VA (1967) Tropical ulcers. *Br Med J* **1**(5535): 283–285.
53. Lupi O *et al.* (2006) Tropical dermatology: bacterial tropical diseases. *J Am Acad Dermatol* **54**(4): 559–578.
54. Serrano-Jaén L and Vega-López F (2000) Fulminating septicaemia caused by *Vibrio vulnificus*. *Br J Dermatol* **142**: 386–387.
55. Cribier B *et al.* (1994) Staphylococcal scalded skin syndrome in adults. *J Am Acad Dermatol* **30**: 319–324.
56. Belsey MA and LeBlanc DR (1975) Skin infections and the epidemiology of diphtheria: acquisition and persistence of *C. diphtheria* infections. *Am J Epidemiol* **102**: 179–184.
57. Matteelli A *et al.* (1994) Short report: verruga peruana in an Italian traveller from Peru. *Am J Trop Med Hyg* **50**(2): 143–144.
58. Thangaraj HS *et al.* (1999) *Mycobacterium ulcerans* disease; Buruli ulcer. *Trans R Soc Trop Med Hyg* **93**: 337–340.
59. Stenos J *et al.* (2005) A highly sensitive and specific real-time PCR assay for the detection of spotted fever and typhus group Rickettsiae. *Am J Trop Med Hyg* **73**(6): 1083–1085.
60. Holman RC *et al.* (2001) Analysis of risk factors for rocky mountain spotted fever: evidence for superiority of tetracyclines for therapy. *J Infect Dis* **184**: 1437–1444.
61. Masters EJ *et al.* (2003) Rocky mountain spotted fever – a clinician's dilemma. *Arch Intern Med* **163**: 769–774.
62. Purvis JJ and Edwards MS (2000) Doxycycline use for rickettsial disease in pediatric patients. *Pediatr Infect Dis J* **19**: 871–874.
63. Parola P *et al.* (2005) Tick-borne rickettsioses around the world: emerging diseases challenging old concepts. *Clin Microbiol Rev* **18**(4): 719–756.
64. McGinnis MR *et al.* (2001) Sporothrix schenckii sensitivity to voriconazole, itraconazoleand amphotericin B. *Med Mycol* **39**: 369–371.
65. Stalkup JR *et al.* (2002) Disseminated cutaneous sporotrichosis treated with itraconazole. *Cutis* **69**: 371–374.
66. Sterline JB and Heymann WR (2000) Potassium iodide in dermatology: a 19th century drug for the 21st century-uses, pharmacology, adverse effectsand contraindications. *J Am Acad Dermatol* **43**: 691–697.
67. Kauffman CA *et al.* (2000) Practice guidelines for the management of patients with sporotrichosis. For the Mycoses Study Group. Infectious Diseases Society of America. *Clin Infect Dis* **30**: 684–687.

68. Ramos-e-Silva M *et al.* (2007) Sporotrichosis. *Clin Dermatol* **25**(2): 181–187.
69. Ramos-E-Silva M and Saraiva Ldo E (2008) Paracoccidioidomycosis. *Dermatol Clin* **26**(2): 257–269.
70. Monsel G and Caumes E (2008) Recent developments in dermatological syndroms in returning travellers. *Curr Opin Infect Dis* **21**: 495–499.
71. Cork MJ *et al.* (2009) Epidermal barrier dysfunction in atopic dermatitis. *J Invest Dermatol* **129**(8): 1892–1908.
72. Nosbaum A *et al.* (2009) Allergic and irritant contact dermatitis. *Eur J Dermatol* **19**(4): 325–332.
73. Bikowski J (2009) Facial seborrhoeic dermatitis: a report on current status and therapeutic horizons. *J Drugs Dermatol* **8**(2): 125–133.
74. Remitz A and Reitamo S (2009) Long-term safety of tacrolimus ointment in atopic dermatitis. *Expert Opin Drug Safety* **8**(4): 501–506.
75. Roelofzen JH *et al.* (2007) Coal tar in dermatology. *J Dermatol Treat* **18**(6): 329–334.
76. Luelmo-Aguilar J and Santandreu MS (2004) Folliculitis: recognition and management. *Am J Clin Dermatol* **5**(5): 301–310.
77. Elston DM (2009) Topical antibiotics in dermatology: emerging patterns of resistance. *Dermatol Clin* **27**(1): 25–31.
78. Ghali F *et al.* (2009) Changing the face of acne therapy. *Cutis* **83**(2 Suppl.): 4–15.
79. Nestle FO *et al.* (2009) Psoriasis. *New Engl J Med* **361**(5): 496–509.
80. Poonawalla T and Kelly B (2009) Urticaria: a review. *Am J Clin Dermatol* **10**(1): 9–21.
81. Frigas E and Park MA (2009) Acute urticaria and angioedema: diagnostic and treatment considerations. *Am J Clin Dermatol* **10**(4): 239–250.
82. Lee AD and Jorizzo JL (2009) Optimizing management of actinic keratosis and photodamaged skin: utilizing a stepwise approach. *Cutis* **84**(3): 169–175.
83. Tierney EP and Hanke CW (2009) Cost effectiveness of Mohs micrographic surgery: review of the literature. *J Drugs Dermatol* **8**(10): 914–922.
84. Statistical Information Team Cancer Research UK (2010) http://www.cancerresearchuk.org/cancer-info/cancerstats/types/skin/incidence/uk-skin-cancer-incidence-statistics (accessed 8 September 2012).
85. Thompson JF *et al.* (2005) Cutaneous melanoma. *Lancet* **365**: 687–701.
86. Botto NC and Warshaw EM (2008) Solar urticaria. *J Am Acad Dermatol* **59**(6): 909–920.
87. Tutrone WD *et al.* (2003) Polymorphic light eruption. *Dermatol Ther* **16**: 28–39.
88. Korting HC and Schollmann C (2009) Current topical and systemic approaches to treatment of rosacea. *J Eur Acad Dermatol Venereol* **23**(8): 876–882.
89. Vedove CD *et al.* (2009) Drug-induced lupus erythematosus. *Arch Dermatol Res* **301**(1): 99–105.
90. Bano S *et al.* (2006) Lupus erythematosus and the skin. *Clin Exp Rheumatol* **24**(1 Suppl. 40): S26–S35.
91. Callen JP and Wortmann RL (2006) Dermatomyositis. *Clin Dermatol* **24**(5): 363–373.
92. Kostler E and Wollina U (2005) Therapy of porphyria cutanea tarda. *Expert Opin Pharmacother* **6**(3): 377–383.
93. Lehman JS *et al.* (2009) Lichen planus. *Int J Dermatol* **48**(7): 682–694.
94. Stein KR and Scheinfeld NS (2007) Drug-induced photoallergic and phototoxic reactions. *Expert Opin Drug Safety* **6**(4): 431–443.
95. Faber WR *et al.* (2006) *Imported Skin Diseases*. Elsevier, Maarssen.

Chapter 13 Travellers' diarrhoea

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Introduction

Travellers' diarrhoea is one of the most common health problems affecting travellers. Economic loses due to travellers' diarrhoea impact both the business and vacationing traveller. The syndrome occurs in 20–50% of travellers, resulting in considerable morbidity of untreated disease [1]. Fortunately, mortality due to typical travellers' diarrhoea is extremely uncommon [2]. Nearly 25% of persons with travellers' diarrhoea change their itinerary, about 15% are confined to bed for a day and approximately 1% of sufferers are admitted to hospital [1]. A whole trip may be ruined by a particularly severe case. Furthermore, 5–10% of those contracting travellers' diarrhoea will go on to develop irritable bowel syndrome. Travellers' diarrhoea is preventable and should be thoroughly addressed when giving medical travel advice. New approaches to prevention and self-treatment with antimicrobial agents have modified the course and impact of this disease substantially [3, 4]. Effective vaccine development remains an area of active research.

General considerations

Travellers' diarrhoea has many fanciful monikers: Montezuma's revenge, Aztec two-step, Delhi belly, Gyppy tummy, Turkey trots and turista. In research studies the syndrome is usually defined as the passage of three or more unformed stools in a 24 hour period plus at least one symptom of enteric disease, such as abdominal pain, cramps, nausea, vomiting, fever or tenesmus [1, 5]. Less severe forms of the syndrome (e.g. 1–2 loose stools per day) can be caused by the same enteropathogens but probably do not need to be treated symptomatically or specifically because they are mild and short-lived [6]. Some definitions of diarrhoea consider the volume of unformed stool passed over a period of time. Such a definition might fail to account for classic dysentery in which many small-volume, bloody, mucoid stools are passed. The total volume of dysenteric stools might not meet the volume definition of diarrhoea. Travellers' diarrhoea lasting longer than 2 weeks, by definition, is persistent diarrhoea and after 4 weeks, chronic diarrhoea.

Travellers might decide to treat illness even though it does not meet the standard definition of diarrhoea. For instance, a traveller might treat one large-volume watery stool associated with a severe cramp. Advice about how to begin self-therapy must be practical and should not be driven simply by study criteria.

Travelers may experience benign changes in bowel movement consistency or frequency due to changes in dietary habits (e.g. increased fruit/vegetable consumption, fat intake, irritating spices and alcohol) and stress. Watery stools can be passed following ingestion of alcohol or associated with menstruation. Although troublesome, most patients and experts do not address these episodes as 'travellers' diarrhoea'.

Aetiology

The frequency with which specific microorganisms cause disease varies somewhat around the world (Table 13.1), but the majority of the identified causal organisms are bacterial [7]. The most common cause of travellers' diarrhoea is *Escherichia coli*, including enterotoxigenic (ETEC), enteroaggregative *E. coli* (EAEC) and enteropathogenic (EPEC). In some regions of the world (e.g. Southeast Asia) *Campylobacter jejuni* is a relatively common cause of travellers' diarrhoea, especially during the winter season. Invasive bacterial pathogens (*Shigella*, *Salmonella* and *Campylobacter*) on average cause more severe, longer-lasting disease than that caused by ETEC. *Salmonella typhi* and *Vibrio cholerae*, both

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Table 13.1 Regional distribution of pathogens causing travellers' diarrhoea (%)*

Pathogen	Latin America	Africa	South Asia	SE Asia
No pathogen identified	49	44	39	50
Bacterial				
Escherichia coli				
Enterotoxigenic	34	31	31	7
Enteroaggregative	24	2	16	ND
Enteropathogenic	14	8	ND	18
Campylobacter jejuni	3	5	8	32
Salmonella spp	4	6	7	9
Shigella spp	7	9	8	2
Plesiomonas shigelloides	1	3	5	5
Aeromonas spp	1	3	3	3
Viral				
Rotavirus	7	7	5	4
Norovirus	17	13	ND	3
Parasitic				
Giardia lamblia	1	2	6	6
Entamoeba histolytica	1	1	4	2
Cryptosporidium	2	1	3	1

ND = no data.
*Adapted from Shah *et al.*, 2009. (Data were rounded to the nearest whole number).

potentially deadly causes of diarrhoea, are uncommon causes of travellers' diarrhoea.

Viruses (e.g. rotaviruses, norovirus, adenoviruses, caliciviruses and other small round viruses) are less common causes of travellers' diarrhoea compared with bacteria. Specific antimicrobial therapy for viral diarrhoea is not available, but bismuth subsalicylate preparations have been somewhat effective in treating some viral causes of diarrhoea. Using non-antimicrobial symptomatic medications such as loperamide likely affords some relief when the cause of diarrhoea is viral. This is one reason why combination therapy with loperamide plus an antimicrobial agent was studied as empiric treatment of the travellers' diarrhoea syndrome.

Parasites are an uncommon cause of travellers' diarrhoea in the developing world [7]; therefore, their treatment need not be included in the self-therapy regimen for most travellers. When trekkers in eastern Europe and Russia might be far removed from medical care, arming them with medication (e.g. metronidazole or tinidazole) to treat possible *Entamoeba histolytica* or *Giardia lamblia* disease is controversial but seems reasonable. In Nepal, *Cyclospora* can cause disease with some regularity. This organism responds only to trimethoprim-sulfamethoxazole. Nitazoxanide has activity against *Cryptosporidium* but has not been well studied in travellers. Since the advent of polymerase chain reaction (PCR) testing of stool for *Cryptosporidium* this organism has been recognised to be present among those with travellers' diarrhoea more commonly than previously thought; it should be considered in those failing to respond to empiric antibiotics. Amoebiasis should also be considered in a traveller to an endemic area who has bloody diarrhoea that fails to respond to antibiotics, but the organism is not a common cause of diarrhoea in short-term travellers.

Many cases of travellers' diarrhoea occur without an obvious known aetiology [7]. Also, new causes of travellers' diarrhoea have been discovered (e.g. enteroinvasive and enteroaggregative *E. coli*) and the role of other enteric organisms is being investigated (e.g. toxin-producing *Bacteroides fragilis* or *Klebsiella*). As a general rule, clinical disease associated with no identified pathogen has responded to antimicrobial agents, implying that a substantial proportion of this subset of travellers' diarrhoea will eventually be found to be caused by bacterial enteropathogens.

Epidemiology

The incidence of travellers' diarrhoea is highest among persons moving from developed to developing countries, with some variation in risk among developing countries [2].

The risk of travellers' diarrhoea averages less than 4% in developed areas such as the United States, Canada, Europe, Australia, New Zealand and other industrialised nations. The risk increases to 8–15% in China, Russia, Middle East, South Africa, certain Caribbean Islands like Jamaica, and the touristic destinations of Thailand. The risk is highest (approximately 40%) in the rest of Africa, Latin America and Southern Asia [2]. The risk of diarrhoea for a person moving from one developed country to another is about the same as it is for a traveller moving from a developing country to a developed country.

Prior experience as a short-term traveller to high-risk areas does not appear to confer much, if any, protection. Expatriates residing in Nepal for a prolonged period of time appear to remain substantially at risk for travellers' diarrhoea. Conversely, the rate of diarrhoea dropped among US adult medical students as they became long-term residents in Mexico, implying that a degree of protection (whether by immunity or risk avoidance) might develop in some expatriate populations [6]. Such protection was measurably lost when medical students returned to Mexico after a 6- to 8-week vacation in the US. The implication is that continued exposure to enteropathogens in a developing country might be necessary for protection against disease to persist. Also, persons who reside in a developing country and move to another developing country appear to have a degree of protection against the development of diarrhoea, because their rates of diarrhoea are lower compared with those of travellers coming from industrialised countries.

Studies of Swiss and Austrian travellers have indicated that 90% of travellers' diarrhoea occurs during the first 2 weeks of stay in a developing country. On the other hand, studies of diarrhoea prevention and prospective 1-month studies of diarrhoea incidence among adults newly arrived in Mexico [6] have indicated that the first-month rate of diarrhoea among US college-age students living in Mexico was 54%. Fifty-seven per cent of the cases occurred in the first 2 weeks of stay in Mexico and 43% of the cases occurred in the second 2 weeks of stay. Such studies help to explain the wide variation in the reported incidence of travellers' diarrhoea. By definition, incidence numbers must include the time of stay in the developing country to be valid.

Perhaps because they consume indiscriminately, the very young are at increased risk for travellers' diarrhoea. Young adults in the 20–29-year age group have the next highest risk. This group is probably fairly adventuresome and willing to sample foods and beverages indiscriminately. They often travel on a shoestring budget and might not have received advice about risk factors and their avoidance. Residing in high- or low-budget hotels has no apparent bearing on the risk of travellers' diarrhoea, perhaps attesting to the ubiquity of the risk. Failure to adhere to dietary advice appears to be universal behaviour that is not limited to the younger age groups.

Some enteropathogens are more likely to cause disease during certain seasons. Among Finnish tourists, *Campylobacter* and *Salmonella* caused disease in Morocco more often in the winter than the autumn, and ETEC causes disease more often in the autumn than the winter. Similarly, *Campylobacter* causes diarrhoea among US adults in Guadalajara, Mexico, predominantly in the winter dry season, and ETEC causes diarrhoea in the summer rainy season [5]. When an effective vaccine becomes available, these observations might be helpful in deciding which short-term travellers to vaccinate against ETEC.

Seasonality of pathogen occurrence does not guide adequately the choice of an antibiotic for the treatment of travellers' diarrhoea. *Campylobacter* disease, for instance, can occur in the 'off' season, and its inherent resistance to an antibiotic such as trimethoprim-sulfamethoxazole is more important than seasonality when choosing an antibiotic for empiric treatment. Increasing antimicrobial resistance worldwide among many enteropathogens, including common *E. coli*, is pivotally important when choosing an antimicrobial agent for empiric use.

Risk factors

Food and, to a lesser extent, water consumption are well-documented risk factors for travellers' diarrhoea. The problem is ingestion of faecally contaminated food or water. Sometimes dirty hands or insects (e.g. flies) are the vectors for faecal contamination of food. Other important risk factors are host-related (e.g. immune status, gastrointestinal disease and behaviour) and should be taken into consideration when counselling patients and when considering chemoprophylaxis.

Water

Travellers should take care to drink safe beverages, even though contaminated water usually accounts only for a minority of travellers' diarrhoea. Tap water in developing countries can be chlorinated, but cross-contamination can occur after water leaves the chlorinating plant. Tap water was the probable vehicle of transmission of predominately non-bacterial diarrhoea in Mexico during the winter [6]. Infection with *Salmonella typhi* has been related to ingestion of contaminated food and water or other non-carbonated beverages. Fortunately, typhoid fever is rare among travellers. Cryptosporidiosis is probably acquired via ingestion of contaminated water. The number of cysts necessary to cause cryptosporidiosis is small, but the level of contamination of

chlorinated water is also usually low. Overall, it is an infrequent cause of travellers' diarrhoea.

Travellers should avoid swimming in freshwater rivers and lakes, which might be a sewer for the local population. Also, salt water can be contaminated by a river emptying into it nearby or by emptying recreational boat bilge near swimming areas. Adequate chlorination and acidification of pool water is not always found in countries without high standards of public health practices.

While firm data are lacking, the risk of diarrhoea is probably not high when ice is made in a machine with clean water. Slab ice is more likely to be or become contaminated. Unwashed hands can contaminate ice in the process of chipping off portions for beverages. Alcohol in a drink cannot be assumed to have sterilised ice. The concentration of alcohol used in mixed drinks takes far more time to kill microorganisms than the time taken to consume the drink. The tiny amount of water involved with brushing teeth or taking a shower is probably a safe exposure, especially if the water is hot.

Food

The use of human excreta as fertiliser, inadequate public health practices and poor personal hygiene of food handlers jeopardise the food hygiene chain in developing countries. Fresh salads have been incriminated consistently as a risk for travellers' diarrhoea. Ideally, produce should be rinsed thoroughly, soaked in a halide solution or similar disinfectant and rinsed in clean water. Kitchen personnel must wash their hands properly after defaecation. The riskiest foods are generally raw and moist. Dry foods are generally safe because microorganisms do not grow well on a dry surface. An especially risky setting appears to be the buffet. Food is usually kept at room temperature for long periods of time, leading to bacterial overgrowth and exposure to contaminated hands and surfaces.

Cooked food is usually safe to eat once the temperature at its interior has reached 70°C (160°F). Enterohemorrhagic *E. coli* can contaminate ground meat at the processing plant. The cook can introduce microorganisms into the middle of a hamburger patty during its preparation. Thorough cooking is critical. Ice cream and other frozen or unfrozen dairy products can also be contaminated and cause disease.

Host-related factors

Differences in host susceptibility to travellers' diarrhoea have been difficult to demonstrate by classical epidemiologic means. Persons with blood group O appear to be more susceptible to cholera but not to ETEC, even though the heat-labile enterotoxin of *E. coli* is similar immunologically to cholera toxin. Emerging genetic data, however, are beginning to unravel some predispositions to diarrhoea. A certain genotype in the lactoferrin gene appears associated with development of diarrhoea in Mexico. A single-nucleotide polymorphism in the gene encoding osteoprotegerin, an anti-inflammatory protein, is also associated with travellers' diarrhoea, especially when it was caused by non-secretory bacterial pathogens. Subjects with polymorphism in the interleukin 8 promotor region appear to be more susceptible to enteroaggregative *E. coli*.

Achlorhydria is a risk factor for travellers' diarrhoea. Stomach acid decreases the inoculum of ingested pathogens to a number that is incapable of causing disease in most instances. An exception is *Shigella*, which is still pathogenic when less than 100 organisms survive stomach acid. H2 blockers and proton pump inhibitors are thought to be risks for diarrhoea because they inhibit acid strongly for prolonged periods, including meal times. The role of antacids as a risk factor for travellers' diarrhoea is less certain, particularly if they are used only well after ingestion of food.

Patients with AIDS and CD4+ counts less than 200 are known to be susceptible to *Salmonella*. After institution of highly active antiretroviral therapy, patients feel better and are more likely to travel. Rises in CD4+ cells should be sustained over at least a 3-month period before the patient can assume they are protected from opportunistic infections to which they would have been susceptible at their nadir. While data are lacking, AIDS patients who travel might be considered for diarrhoea chemoprophylaxis if their CD4+ count is less than 200. Other immune-deficient hosts, such as patients receiving cancer chemotherapy or corticosteroids, as well as those with common IgA deficiency should also be considered to be at special risk for the development of travellers' diarrhoea.

Some hosts are not necessarily more at risk of developing diarrhoea, but when they do develop it the consequences are worse compared with the average host. Such persons include those with underlying gastrointestinal diseases, such as Crohn's disease and ulcerative colitis, and persons with an ileostomy. Dehydration in such patients is an important concern. Elderly patients with diarrhoea might become confused and forget to rehydrate themselves or they might continue diuretic therapy in the face of developing dehydration. Small children and infants are at special risk of becoming dehydrated when they develop diarrhoea. On the other hand, travellers' diarrhoea in the healthy adult is usually not dehydrating [5].

Adventurous travellers are difficult to advise. They may plan to eat indiscriminately and might ask for chemoprophylaxis against diarrhoea. Such patients serve to remind us

that we should not be overly judgrmental about quality-of-life decisions as long as such persons are fully informed about the risks and benefits of medications and behavioural change.

Salient clinical features

Travellers' diarrhoea is a clinical syndrome. The clinical manifestations of the various microbiological causes of travellers' diarrhoea overlap considerably [8]. It usually begins within 2–3 days of arrival to the destination. The average frequencies of associated symptoms are: cramps, 40–60%; nausea, 10–70%; vomiting, 5–10%; and fever, 10–30%. Because of considerable overlap in the clinical syndromes categories of diarrhoea such as 'secretory' or 'invasive' do not adequately differentiate the specific aetiology of diarrhoea in an individual. Patients infected with a classic invasive pathogen such as *Shigella* often present early with watery diarrhoea and not the frequent, small-volume, bloody and mucus-laden stools that characterise dysentery. Alternatively, patients infected with a classic secretory pathogen such as ETEC can sometimes present with low-grade fever and a small amount of occult blood in the stool. The more severe the diarrhoea, the more likely that an invasive pathogen will be found, but the relationship is not strong enough for clinical decision making in the individual patient [8]. Cholera usually presents as a very high output 'rice water' diarrhoea with low-grade temperature and quickly leads to life-threatening dehydration. Patients should be advised to seek prompt medical help when such characteristics are present.

Management, treatment and control

General principles

Some authorities feel that symptomatic or specific therapy of travellers' diarrhoea is frequently not necessary because travellers' diarrhoea is a self-limiting disease; fluid and electrolyte replacement is the preferred approach to diarrhoea management. Electrolyte replacement solutions are increasingly readily available in pharmacies or grocery stores in developing countries. An antimicrobial agent might be used when results of a stool culture show that the cause of diarrhoea is an invasive pathogen. However, a well-trained physician, who also speaks the traveller's language and understands appropriate treatment of travellers' diarrhoea, may be difficult to locate in a developing country. Delay in treatment while waiting for stool culture results can increase time lost from planned activities. Finally, many of the enteropathogens associated with travellers' diarrhoea require a research laboratory to identify.

Another approach to therapy is to reserve empirical antibiotic treatment for occasions when clinical parameters suggest disease caused by an invasive pathogen. The problem is that neither patients nor physicians can reliably predict when an invasive pathogen is causing disease based solely on clinical symptoms and signs. While the positive predictive power of symptoms of dysentery is high, the negative predictive power is low. If only patients with dysentery were treated with an antibiotic, many patients with disease caused by an invasive pathogen would be denied the benefits of antibiotics.

Empiric self-therapy, regardless of the cause of diarrhoea, has emerged as a valid approach to the treatment of travellers' diarrhoea [1, 5]. Choice of a specific antimicrobial agent has been determined, in part, by a growing understanding of the many causes of travellers' diarrhoea and increasing antimicrobial resistance among some of the enteropathogens [4].

Oral rehydration therapy and feeding

Oral rehydration solution is a cost-effective, elegantly simple treatment for dehydrating diarrhoea. The addition of glucose to electrolyte-containing solutions facilitates absorption of electrolytes. The output of fluid is increased by as much as 50% by aggressive fluid replacement with traditional oral rehydration solutions. Furthermore, travellers' diarrhoea is not usually a dehydrating disease. The addition of oral rehydration solution to therapy with loperamide makes no difference to the recovery of the patient with usual travellers' diarrhoea. The use of oral rehydration solutions that contain complex sugars derived from rice or cereal can lower the output of diarrhoea, and such solutions should be studied in the treatment of travellers' diarrhoea.

Early refeeding is recommended in children with diarrhoea. In adults, stringent dietary adjustment was found not to be necessary, likely because diarrhoea abated so quickly with contemporary therapy. When symptoms linger despite treatment, common sense suggests that milk, fruits, vegetables, red meat, caffeine and alcohol should be added to the diet only when diarrhoea has abated. Persisting or recurring symptoms should prompt consideration of parasitic disease.

Antimicrobial therapy

Kean first demonstrated the successful prevention of travellers' diarrhoea with antimicrobial agents in 1962 [9]. Many

studies have verified the efficacy of antimicrobial agents in both the prevention and the treatment of the syndrome. Antibiotics can limit the course of diarrhoea to approximately 1 day. Untreated diarrhoea lasts more than 3 days. The benefits of antibiotic therapy include significant reductions in the total duration of diarrhoea, earlier relief of accompanying symptoms like cramps, and a decrease in the amounts of time spent in bed and missing or altering planned activities. Some experts still consider that antibiotics have little role in the empiric treatment of travellers' diarrhoea. While it is true that travellers' diarrhoea is a self-limited disease, in the author's opinion and in the judgement of recent guidelines and an evidence-based review, the considerable relief afforded by antibiotic treatment argues against therapeutic nihilism [4, 10].

A number of antibiotics have been shown to be useful in the treatment of travellers' diarrhoea. For years trimethoprim-sulfamethoxazole (TMP-SMX) was an excellent choice for treatment, and trimethoprim alone could be substituted for patients who were allergic to sulfa preparations. TMP-SMX resistance around the world has increased so much that it is no longer a preferred empiric treatment choice.

Fluoroquinolones such as norfloxacin, ciprofloxacin, ofloxacin, enoxacin, fleroxacin and others demonstrate considerable activity against most enteropathogens and efficacy in general in the empiric treatment of travellers' diarrhoea (Table 13.2). All fluoroquinolones appear to be highly effective, so the choice of one should probably be based solely on the price. The problem with fluoroquinolones is increasing resistance among *Campylobacter* such that a fluoroquinolone is no longer the antimicrobial agent of empiric choice in Southeast Asia. Other enteropathogens are beginning to show increasing resistance, implying the continuing usefulness of the fluoroquinolones in the empiric treatment of travellers' diarrhoea may be limited.

In the US, the poorly absorbed antibiotic rifaximin has been approved for use in the treatment of travellers' diarrhoea but not when invasive pathogens are thought to be the cause. The theoretic reasons for preferring non-absorbed agents are that they should engender fewer side effects and should be safer to use in children and pregnant women, in whom the currently preferred quinolones are contraindicated. With the exception of rifaximin, which is available in some countries but not worldwide, companies have been slow to develop such agents further.

Erythromycin is somewhat effective in *Campylobacter* disease and has been shown to be effective in the prevention of travellers' diarrhoea, probably owing to its activity against Gram-negative enteric organisms in the alkaline milieu of the gut. Erythromycin, however, has not been studied for the treatment of travellers' diarrhoea. The azalide azithromycin has much better activity against Gram-negative enteric organisms and is effective in the treatment of *Campylobacter* disease and travellers' diarrhoea in general. Azithromycin has emerged as the drug of choice for the empiric treatment of travellers' diarrhoea in Southeast Asia, where *Campylobacter* is the predominate pathogen.

Certain antibiotics are available over the counter in many developing countries and local physicians might recommend them. These include ampicillin, which is simply not active enough around the world to be an effective choice. Furazolidone is active not only against bacterial causes of travellers' diarrhoea but also against *Giardia*. The problem is that furazolidone is only about one-half as effective as the quinolones

Table 13.2 Antimicrobial agents recommended for the treatment of travellers' diarrhoea

Agent	Dose	Comments
Trimethoprim-sulfamethoxazole	Two DS[a] tablets as a single dose One DS tablet twice daily for 3 days	A loading dose regimen led to a statistical benefit that was not clinically relevant. Rising resistance worldwide has limited its usefulness
Fluoroquinolones		
Norfloxacin	400 mg twice daily for 3 days	Higher doses can be used for single-dose therapy. Fleroxacin is also effective in travellers' diarrhoea and other fluoroquinolones like pefloxacin should also be effective
Ciprofloxacin	500 mg twice daily for 3 days	
Ofloxacin	200 mg twice daily for 3 days	
Levofloxacin	500 mg daily for 3 days	
Azithromycin	500 or 1000 mg as a single dose	Highly effective agent in recent studies. Higher dose is preferred when *Campylobacter* is suspected
Rifaximin	200 mg thrice daily for 3 days	Not absorbed

[a]Trimethoprim-sulfamethoxazole DS = 160 mg TMP plus 800 mg SMX.

in the treatment of the common bacterial causes of travellers' diarrhoea.

Increasing resistance around the world has limited the usefulness of doxycycline. Chloramphenicol is cheap and readily available over the counter in many countries; however, its rare but devastating bone marrow toxicity limits its widespread recommendation. Clioquinol was studied many years ago with variable results. It was taken off the market in many countries because of serious ophthalmologic adverse effects. Doxycycline, chloramphenicol and clioquinol cannot be recommended.

The duration of treatment with antibiotics has steadily decreased with ongoing study. Now a single dose of antibiotic can be recommended for most patients [1, 4, 10, 11]. The invasive pathogens and severe disease are the causes and clinical state that might require lengthier therapy than a single dose. As a rule, *Shigella* responds to single-dose therapy, but disease caused by *S. dysenteriae* appears best treated with a 3-day course of antibiotic. Fortunately, *S. dysenteriae* is an uncommon cause of travellers' diarrhoea. While a single 1000 mg dose of azithromycin can be recommended for *Campylobacter* disease, this dose amounts to giving a longer duration of therapy owing to the long half-life of azithromycin. Although data are lacking, any other agent should probably be dosed for at least 3 days when treating *Campylobacter*.

Depending on the destination, we provide clients with 3-day courses of a fluoroquinolone (much of the world) or a single 1000 mg dose of azithromycin (preferred for Southeast Asia) for self-therapy [12]. When travellers use a fluoroquinolone we ask them to re-evaluate themselves at the end of 24 hours when the next dose of antibiotic would be due. If they are still passing unformed stools, or fever or passage of bloody stools was a feature of their disease, we recommend that they finish the full 3 days of antibiotic; otherwise, we feel that short-course antibiotic therapy suffices.

Symptom management

Less severe disease can be treated with a variety of non-antibiotic agents (Table 13.3). Bismuth subsalicylate (BSS)-containing compounds decrease the number of unformed stools passed after beginning treatment by 16–18%. The antisecretory and antimotility agent loperamide is more efficacious than BSS and decreases the number of stools by more than 50%. Neither is as effective as an antibiotic.

Some studies with antimotility agents such as diphenoxylate suggested that the agents might prolong the course of disease caused by invasive enteropathogens. In a small number of prisoners, shigellosis was treated with an antibiotic and diphenoxylate. Shedding of *Shigella* and fever were prolonged. Patients with bloody diarrhoea treated with diphenoxylate alone had a longer course of disease than did placebo-treated subjects. The use of antimotility agents should be avoided in the treatment of *Clostridium difficile* disease. Conversely, current research indicates disease is not prolonged when patients are able to take an antibiotic when they feel they are not getting enough relief from loperamide. Also, ciprofloxacin plus loperamide treats *Shigella* dysentery more effectively than ciprofloxacin alone [13].

Table 13.3 Symptomatic treatment of travelers' diarrhoea

Therapeutic agent	Dose	Comments
Attapulgite	3 g initially and after each loose stool for a total of 9 g per day	Safe in pregnancy but only marginally effective
Bismuth subsalicylate preparations	30 ml (1 ounce) every half-hour for a total of 240 ml (8 ounces)	Rinse mouth carefully. Brush teeth and tongue after evening dose
Loperamide	4 mg loading dose, then 2 mg after each loose stool, not to exceed 16 mg per day	Over-the-counter directions limit total daily dose to 8 mg. Oral hydration does not add to symptomatic relief afforded by loperamide

Loperamide is absorbed rapidly and acts more quickly than BSS preparations, which take nearly 4 hours to begin having their effect. Loperamide is a safe drug that is available over the counter. It is approved for use in children as young as 3 years old.

The prescription product diphenoxylate plus atropine (Lomotil) is popular, but the drug is not as efficacious as loperamide in the treatment of diarrhoea and has a relatively unfavourable side effect profile. Elderly men can suffer urinary retention due to the atropine. Lomotil is habit forming and central nervous system side effects are possible.

Other symptomatic drugs that have been advocated in the past include the anticholinergic agents, activated charcoal, *Lactobacillus* preparations, polycarbophil, methylcellulose, psyllium and kaolin/pectin preparations. None of these is not effective for the treatment of travellers' diarrhoea with the exception of attapulgite (a hydrated aluminum silicate clay preparation), which performed well enough in trials to recommend it for mild diarrhoea. Attapulgite is a safe

product that can be recommended for use in pregnant women. It causes a more formed stool; however, net losses of water and electrolytes persist unabated.

Recent studies have shown that a new and novel calmodulin inhibitor, zaldaride, is useful in decreasing the duration of diarrhoea from an average of 42 hours in untreated subjects to an average of 20 hours [1]. The drug worked both in ETEC disease and in other bacterial diseases, suggesting a common role for calmodulin for the pathogenesis of diarrhoea. Zaldaride is not marketed worldwide. Yet another agent, the antisecretory drug SP303, showed promise in the symptomatic relief of travellers' diarrhoea but was never marketed.

The combination of an antibiotic and loperamide has been studied with the usual dose of each agent. In one study more than half of the patients passed no further unformed stools once combination therapy was begun. The average duration of diarrhoea was only a few hours, even when patients had blood in stools at enrolment. This result was superior to treatment with either agent alone and was confirmed in subsequent studies [11]. Synergy has been demonstrated with loperamide plus a fluoroquinolone, azithromycin and rifaximin [4]. Some studies have not verified synergistic results, either when *Campylobacter* was a common cause of disease or when disease among placebo controls was relatively mild. Importantly, the combination of loperamide plus ciprofloxacin proved to be safe and superior in efficacy to ciprofloxacin alone in the treatment of shigellosis in Thailand.

Algorithmic approach to treatment

Among all travellers developing diarrhoea, approximately 40% will have mild, self-limiting disease that ceases within a day or two, with passage of no more than two unformed stools per day [5]. Once a third loose stool is passed within a 24 hour period, diarrhoea can be predicted to become more severe and/or last many days. We advise longer-term travellers such as expatriates to withhold antibiotic treatment for travellers' diarrhoea unless more than two loose stools are passed in a day. Some disease begins so explosively that therapy should logically be begun before passage of a third loose stool. Figure 13.1 outlines our approach to the treatment of travellers' diarrhoea.

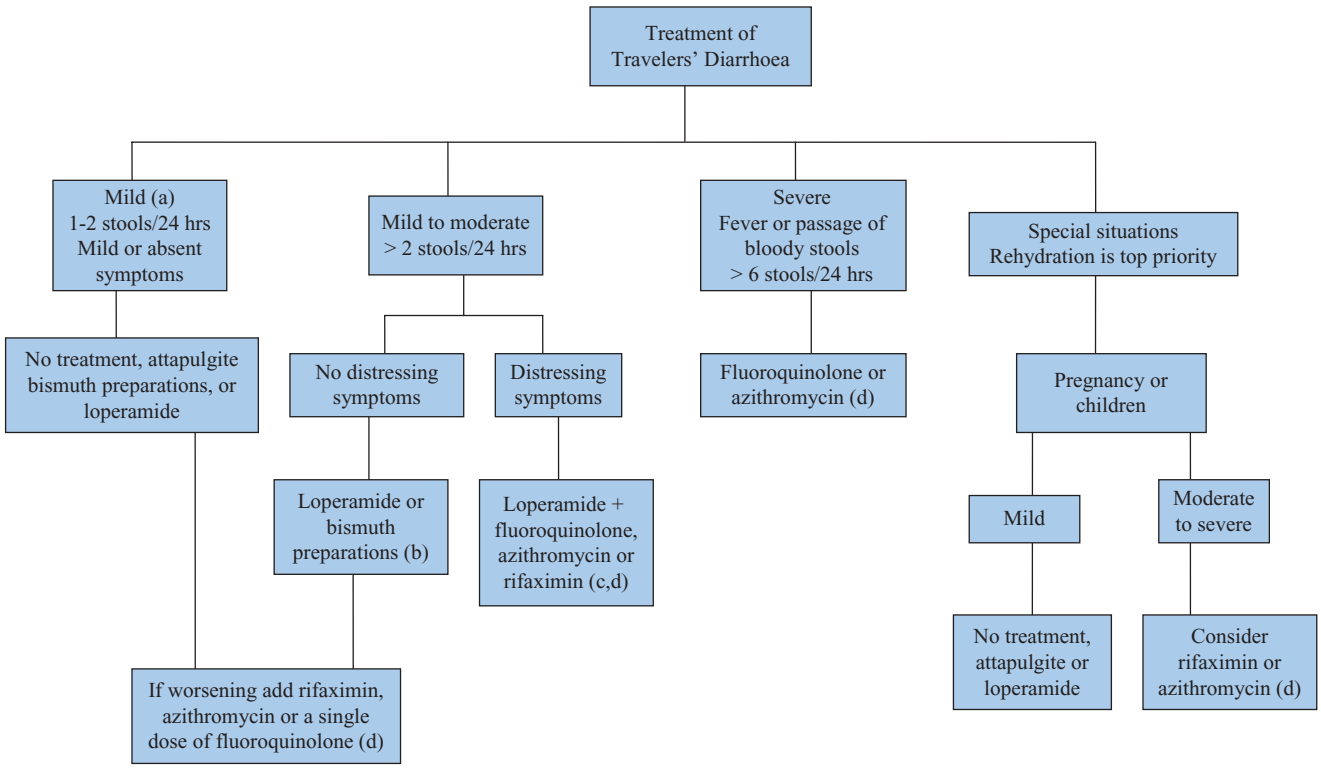

Figure 13.1 Algorithmic approach to the treatment of travellers' diarrhoea. (a) Long-term travellers are encouraged to endure mild diarrhoea to develop some immunity. (b) Business travellers on short, critical trips might consider earlier addition of a single dose of antibiotic. (c) Reassess symptoms when second dose of fluoroquinolone is due. Discontinue therapy if diarrhoea has abated. A single dose of antibiotic usually suffices. (d) Azithromycin is preferred in Southeast Asia where *Campylobacter* is the predominate pathogen. Rifaximin should not be used when diarrhoea is bloody or if invasive pathogens are suspected.

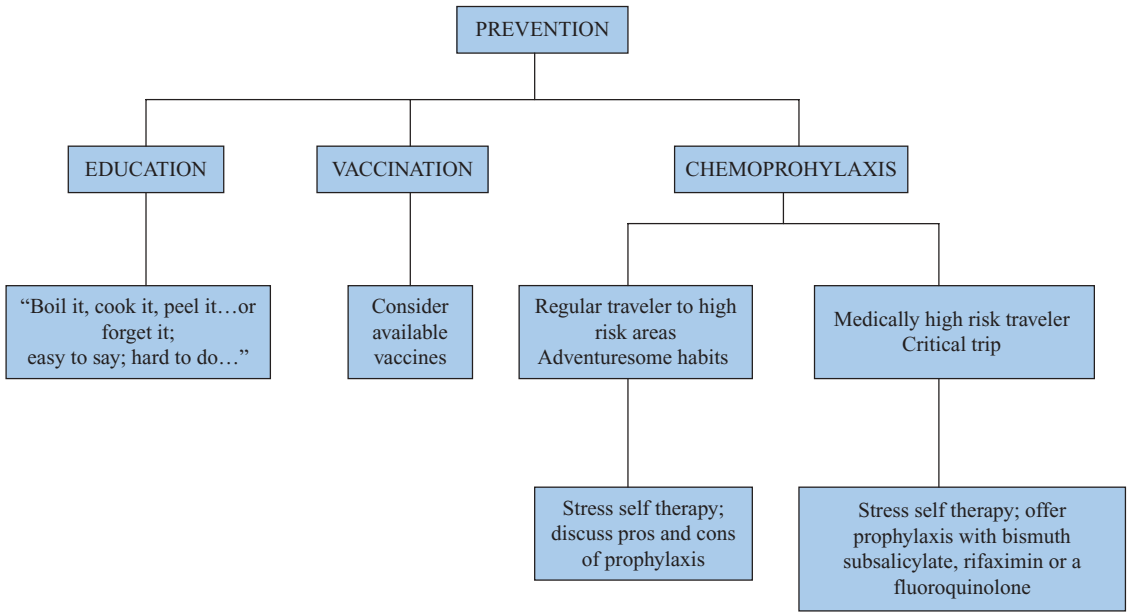

Figure 13.2 Approach to prevention of travellers' diarrhoea.

Health advice and protective measures

As shown in Figure 13.2, options for the prevention of travellers' diarrhoea include education, vaccination and chemoprophylaxis with either BSS-containing compounds or antibiotics. Although vaccination is a promising option, vaccines against all enteropathogens that cause travellers' diarrhoea will probably never be possible or cost-effective owing to the large number of strains that cause disease; arming travellers to treat disease will still be necessary.

Education

The problem with education as an approach to prevention is achieving and maintaining behaviour modification among tourists. The tourist too often has a carefree attitude, wants intentionally to sample new culture and food, and has consumed alcohol, which disinhibits all travellers. Catchy phrases like 'boil it, cook it, peel it – or forget it' are simply not practised. Business travellers appear to have fewer episodes of diarrhoea than do most tourist travellers. The business traveller occasionally faces meals of exotic and risky foods that cannot be refused easily. While not studied, a single dose of an effective antimicrobial should be effective in preventing most causes of diarrhoea after such a risky meal.

Many travel experts have given up trying to educate travellers about safe culinary practices. The problem is that creative efforts at education have not been employed either because of ignorance of behavioural modification techniques and/or too much pressure on the practitioner's time. If travellers visit a specialised travel medicine clinic, time should be devoted to their education. Table 13.4 shows the main specific recommendations to be given regarding food and beverage consumption, as well as eating attitudes.

Chemoprophylaxis

As shown in Table 13.5, BSS-containing compounds can be as much as 65% effective for the prevention of travellers' diarrhoea [3]. Protection rises substantially if travellers are also careful in what and where they eat. BSS is an antimicrobial and also has antisecretory and anti-inflammatory properties. When the daily dose of BSS is taken as two divided doses, it is less effective than when the same total dose is taken as four smaller doses. Chewed tablets are as effective as liquid preparations. Bismuth toxicity is rare with ingestion of BSS. Serum bismuth concentrations are well below the level associated with encephalopathy, even after 2 weeks of use. Salicylate, however, is nearly completely absorbed. Chewing two tablets four times a day approximates taking three to four adult aspirins in terms of the salicylate absorbed. Taking aspirin should be avoided when BSS compounds are taken. Patients taking oral anticoagulants should be

Table 13.4 Dietary advice for avoiding travellers' diarrhoea

	Safe	Probably safe	Unsafe
Culinary practices	Careful Considers heat of food	Recognised restaurants Judicious alcohol intake	Adventurous Vendors Buffet food at room temperature Excessive alcohol
Beverages	Carbonated soft drinks Boiled water Iodised water Irradiated milk	Fresh citrus juices Packaged, machine-made ice Bottled water	Tap water Uncarbonated, bottled fruit juices Chipped ice Unpasteurised milk or butter
Food	Piping hot Peeled fruit Processed/packaged Cooked vegetables	Dry Jelly/syrup Washed vegetables	Cold salads Uncooked, cold sauces Undercooked hamburgers Unpeeled fruit Some cold desserts Fresh soft cheese Raspberries/strawberries

Table 13.5 Comparison of bismuth subsalicylate and antibiotics for the prevention of travellers' diarrhoea

	Major side effects (%)	Minor side effects (%)	Protection against diarrhoea (%)
Antimicrobial agent[a]	0.01	3	~70–80
Bismuth subsalicylate	0	1	~65

[a]Percent protection for fluoroquinolones, trimethoprim-sulfamethoxazole efficacy is lower.

cautioned against the use of BSS. At standard doses of BSS, tinnitus was no more common in subjects who took active drug than in those who took placebo. Black insoluble bismuth salts in stools can be confused with melena. After a bedtime dose of BSS, the tongue should be gently brushed and the mouth carefully rinsed to avoid awakening with a black tongue.

Antibiotics are up to ~80% effective in preventing travellers' diarrhoea as long as they are active against the causal enteropathogens (Table 13.5) [5]. Concentrations of antibiotic in stool are probably the best predictive of activity of antibiotics in preventing or treating enteropathogens. 'High-level' resistance, usually defined in terms of inadequate serum concentrations, predicts clinical ineffectiveness in the treatment and prevention of diarrhoea only if adequate concentrations are also not achieved in stool. Antibiotics that can be recommended at present for the prevention of travellers' diarrhoea are outlined in Table 13.6. Non-absorbed antibiotics are theoretically appealing for the prevention of travellers' diarrhoea because of predictable high efficacy and low potential for adverse reactions. The poorly absorbed (<0.4 %) rifaximin has now been studied in prevention, and it is effective and safe.

A 1985 Consensus Development Conference in Washington concluded that travellers' diarrhoea was self-limiting and did not cause mortality; therefore, antibiotic prophylaxis should not be used owing to rare but severe side effects. Further, the consensus was that BSS should not be used because patients might abuse an over-the-counter preparation.

In our clinic we offer prophylaxis to subjects travelling to high-risk destinations, and we encourage chemoprophylaxis of travellers' diarrhoea in certain high-risk hosts. Our default recommendation is now rifaximin; however, this agent is not available in all countries. Likewise, BSS is not available worldwide. We educate the traveller wanting prophylaxis about the pros and cons of chemoprophylactic agents, stress the benefits of self-treatment and let the traveller make the final decision. Perhaps not surprisingly, in a recent questionnaire study, when North American travellers were offered the option of chemoprophylaxis approximately two-thirds of travellers expressed a preference for prophylaxis; whereas the same proportion of European travellers preferred not to take prophylaxis [14].

Table 13.6 Agents for the prevention of travellers' diarrhoea

Agent	Dosing regimen	Comments
Activated charcoal	Variable	May adsorb important medications; not efficacious, not currently recommended
Lactobacillus and other probiotic preparations	Variable	Safe; efficacy not proven, not recommended
Bismuth subsalicylate preparations	Two 262 mg tablets chewed 4 times a day	Rinse mouth to avoid black tongue; 65% protective; may cause constipation and black stools
Trimethoprim-sulfamethoxazole	One double-strength tablet daily	Resistance rising worldwide; <60% protective
Fluoroquinolones		Approximately 80% protective; generally reserve for self-therapy; other fluoroquinolones should work as well
Norfloxacin	400 mg daily	
Ciprofloxacin	500 mg daily	
Levofloxacin	500 mg daily	
Ofloxacin	300 mg daily	
Rifaximin	200 mg daily	Approximately 70% protection. Pending additional study twice-daily dosing might be more appropriate for prevention of diarrhoea in Southeast Asia where *Campylobacter* is prevalent

The concept of chemoprophylaxis is not straightforward. In addition to possible adverse reactions, the cost of chemoprophylactic agents must be considered. Prophylaxis was found to be more cost-effective than treatment for many travellers, when treatment with an antibiotic took approximately a day to cure the patient. Expensive vacation time was often lost. Treatment with an antibiotic plus loperamide has so shortened the course of disease that vacation time is not often lost when diarrhoea is treated empirically and quickly. Treatment with a single dose of antibiotic and loperamide is more cost-effective than prevention, with the exception perhaps of trips that last only a few days. Chemoprophylaxis may lead to complacency in food and beverage selection, thus adding additional behavioural risks for acquiring parasitic or viral disease against which an antibiotic has no or little activity.

The use of antibiotics can cause overgrowth of *Candida*, resulting in vaginitis. Overgrowth of *Clostridium difficile* can cause diarrhoea and recent reports of fluoroquinolone resistant *C difficile* raise concerns about the use of these agents in chemoprophylaxis. Rifaximin on the other hand is efficacious in the treatment of *C. difficile* enterocolitis. Some antibiotics seem to promote infection with certain organisms such as *Salmonella* and *Campylobacter*.

Early, effective antibiotic treatment can obviate the immune response to an enteropathogen. Expatriates probably should not take chemoprophylaxis to prevent diarrhoea and should not treat mild disease with an antibiotic [6]. This approach might encourage immunity to develop against some enteropathogens. Might tourists using preventative antibiotics in a developing country promote the emergence of antibiotic resistance? Antibiotics (often dosed subtherapeutically) used by indigenous persons in a developing country are probably much more important to the development of resistance than antibiotic use by a relatively small number of tourists.

The bivalent cation in BSS interferes with the absorption of doxycycline. This interaction might jeopardise malaria prevention by lowering serum doxycycline concentrations below effective levels. Since the interaction occurs when the two drugs are taken concomitantly, and since prophylactic BSS is taken four times a day, plenty of opportunity exists for drug–drug interaction. The combination of BSS and doxycycline should be avoided.

Finally, parasites, viruses and *Clostridium difficile* become relatively more likely causes of diarrhoea when a short-term traveller takes a prophylactic antibiotic and still develops diarrhoea. These causes are ideally evaluated in conjunction with a visit to a physician, who can order stool studies in order to prescribe logical treatment. However, empiric treatment with nitazoxanide (followed by trimethoprim-sulfamethoxazole to treat *Cyclospora* if diarrhoea persists) is a consideration for the trekker or others when they are far removed from reliable medical care.

Immunisation

Vaccination to prevent travellers' diarrhoea is limited by the number of available vaccines against the aetiologic agents and their efficacy.

An oral vaccine for prevention of cholera (cholera whole cell/recombinant B subunit) is available in some parts of the world, and it appears to cross-protect somewhat against ETEC disease. Cholera vaccination is not necessary for most tourists,because they are simply not at risk unless they insist on eating raw seafood or are forced to live under deplorable conditions (e.g. some Peace Corps volunteers and refugee workers). Vaccination against typhoid with oral Ty21a or parenteral Vi vaccine is easy and devoid of bothersome side effects. While the vaccine is routinely recommended for travel to developing regions, risk of typhoid is often low among most tourists. Vaccination against *Shigella* and other enteric agents is currently under investigation. A novel LT toxin vaccine administered by skin patch has proven to have cross-over protection against multiple pathogens. This approach holds promise.

New so-called DNA vaccine technology and novel vaccine delivery systems (e.g. fruit and vegetables) promise to revolutionise the field of vaccines and might have an important impact on risks for travellers' diarrhoea in the future.

Milk immunoglobulins against ETEC have provided passive protection for a particular strain. Perhaps due to high development costs, further development of this approach has faltered.

References

1. DuPont HL and Ericsson CD (1993) Prevention and treatment of travelers' diarrhea. *New Engl J Med* **328**: 1821–1827.
2. Castelli F and Black RE (2008) Epidemiology of travlers' diarrhea. In: Ericsson CD, DuPont HL and Steffen R. (eds) *Travelers' Diarrhea*, 2nd edn, pp. 92–104. Decker, Hamilton, ON.
3. DuPont HL *et al.* (2009) Expert review of the evidence base for prevention of travelers' diarrhea. *J Travel Med* **16**: 149–160.
4. DuPont HL *et al.* (2009) Expert review of the evidence base for self therapy of travelers' diarrhea. *J Travel Med* **16**: 161–171.
5. Ericsson CD and DuPont HL (1993) Travelers' diarrhea: approaches to prevention and treatment. *Clin Infect Dis* **16**: 616–624.
6. Ericsson CD *et al.* (1994) Epidemiologic observations on diarrhea developing in US and Mexican students living in Guadalajara, Mexico. *J Travel Med* **2**: 6–10.
7. Shah N *et al.* (2009) Global etiology of travelers' diarrhea: systematic review from 1973 to the present. *Am J Trop Med Hyg* **80**: 609–614.
8. Mattila L (1994) Clinical features and duration of travelers' diarrhea in relation to its etiology. *Clin Infect Dis* **19**: 728–734.
9. Kean BH *et al.* (1962) The diarrhea of travelers. V. Prophylaxis with phthalylsulfathiazole and neomycin sulphate. JAMA: *J Am Med Assoc* **5**(180): 367–371.
10. Hill DR *et al.* (2006) Guidelines for the practice of travel medicine. *Clin Infect Dis* **43**: 1499–1539.
11. Ericsson CD *et al.* (1997) Single dose ofloxacin plus loperamide compared with single dose or three days of ofloxacin in the treatment of travelers' diarrhea. *J Travel Med* **4**: 3–7.
12. Ericsson CD *et al.* (2007) Loperamide plus azithromycin more effectively treats travelers' diarrhea in Mexico than azithromycin alone. *J Travel Med* **14**: 312–319.
13. Murphy GS *et al.* (1993) Ciprofloxacin and loperamide in the treatment of bacillary dysentery. *Ann Int Med* **118**: 582–586.
14. Ericsson CD *et al.* (2009) Travelers' preferences for the treatment and prevention of acute diarrhea. *J Travel Med* **16**: 172–178.

Chapter 14 Vaccine-preventable disease

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Immunisation and vaccination

Vaccination is the process of administering a vaccine as a form of prophylaxis or treatment against disease. Immunisation is the process by which an individual's acquired immune system is enhanced against certain infectious diseases by natural or artificial means. Immunisation can thus provide complete protection against infection from certain diseases or modify the clinical course should an individual become infected, leading to a milder disease with fewer complications. It may be achieved by passive immunisation or much more commonly by active immunisation [1–3].

Passive immunisation is defined as the transfer of preformed immunoglobulin (antibodies) to an individual either by injection of donor antibodies or passive transfer across the placenta from mother to fetus [2]. Although it provides immediate protection against a disease, the levels of antibody are lower than those achieved with vaccination and the duration of protection is limited to a few weeks or months as immunological memory is not elicited [2, 3].

Active immunisation is defined as the stimulation of an individual's acquired immune system against a particular disease by exposure to natural infection or to a vaccine against the disease. Vaccination is the administration of a vaccine which consists of artificially produced antigens that elicit active immunity to a disease [2, 3].

Immunisation also has a role in protecting populations from infections through herd immunity, whereby vaccinated individuals are less likely to be a source of infection to unvaccinated individuals. If vaccination coverage in a population is not maintained then herd immunity can be lost, leading to the re-emergence of disease in the population [4, 5].

Live vaccines

Live vaccines include Bacillus Calmette-Guérin (BCG), measles, mumps and rubella (MMR), oral polio, oral typhoid, varicella and yellow fever (*see* Table 14.1). Live vaccines consist of attenuated microorganisms that, with administration, mimic natural infection, but with significantly reduced virulence so they do not cause illness in most circumstances. They do not require adjuvants and are more likely to induce long-lasting or even life-long immunity following administration of a single dose by activating both the cell-mediated and humoral response.

Inactivated vaccines

Inactivated (killed) vaccines are used when live attenuated vaccines are not available or where reversion of an attenuated strain to wild type occurs with relative ease. Inactivated vaccines do not stimulate infection or mimic disease, are generally less immunogenic, and initially induce a predominantly humoral response which provides less efficient immune protection. A primary course of several doses is usually required to induce a sufficient immune response and regular boosters are then often needed to provide long-lasting immunity through the stimulation of both the cell-mediated and humoral immune systems [2, 3].

Contraindications

Contraindications to vaccination include previous anaphylaxis to a previous dose of the vaccine or any of its constituent components or excipients. Some vaccines, including influenza, yellow fever, tick-borne encephalitis and some

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Table 14.1 Type of vaccines

Live vaccines	Inactivated vaccines	Toxoid vaccines
BCG	Anthrax	Diphtheria
Measles, mumps, rubella	Cholera (oral, parenteral)	Tetanus
	Haemophilus (Hib)	
Oral cholera	Hepatitis A	
Oral poliomyelitis	Hepatitis B	
Oral typhoid	Influenza	
Varicella	Japanese encephalitis	
Yellow fever	Pertussis	
	Plague	
	Pneumococcus	
	Inactivated poliomyelitis	
	Rabies	
	Tick-borne encephalitis	
	Inactivated typhoid	

rabies vaccines, are cultured in purified egg or chick embryo cells. Hypersensitivity to egg is a contraindication to influenza vaccine, and an anaphylactic reaction to egg contraindicates influenza, tick-borne encephalitis and yellow fever vaccines. MMR vaccine is cultured in chick embryo fibroblasts and experience has shown that it is unlikely to contain a sufficient quantity of egg proteins to stimulate a hypersensitivity reaction in those allergic to eggs. However, it is essential that it is administered under extreme caution in a hospital setting to those who are hypersensitive to eggs and chicken protein [6]. Skin testing and graded challenge or desensitisation has been successfully used in those allergic to influenza and yellow fever vaccines but this is not routine practice [7].

Live vaccines are contraindicated in travellers who are pregnant or who are significantly immunosuppressed for any reason. Exceptions to this may include yellow fever vaccination in the third trimester of pregnancy, where the risk of natural infection outweighs the risk of infection from the vaccine. Travellers with HIV may also receive live vaccines with the exception of BCG (regardless of the CD4 count), and yellow fever vaccine if their CD4 is <200 [2].

Immunocompromised travellers

Immunocompromised travellers are at increased risk of certain vaccine-preventable infectious diseases and of certain vaccine adverse events, including uncontrolled live vaccine replication and dissemination. It is important that such individuals are immunised adequately with all indicated and appropriate vaccines and that consideration is given to the requirement of additional booster doses with shorter recommended intervals, as suboptimal immune responses to certain vaccines may occur. Serological testing following vaccination may be considered and may be beneficial in some cases. The timing of immunisation may depend on their level of immunosuppression and, where possible, travellers should be immunised before they become severely immunosuppressed. It may be appropriate to delay immunisation in travellers with temporary immunosupression or travellers whose level of immunosupression may improve with treatment or time, to afford them the opportunity of a better immune response to vaccination [2, 3].

Inactivated and toxoid vaccines can be administered safely to immunocompromised travellers who may mount a suboptimal immune response and may therefore require additional booster doses of vaccine [2]. Generally, all live vaccines are contraindicated in immunocompromised travellers due to the risk of disseminated infection with the live vaccine strain [8]. Live vaccines are contraindicated for at least 1–2 years after the cessation of immunosuppressive treatment for tissue or organ transplant recipients, including bone marrow recipients [2, 9]. Where appropriate, such travellers may require serological testing, for example with regard to MMR, and re-immunisation or further booster doses may be recommended. UK recommendations are that live vaccines are contraindicated in travellers for at least 6 months (3 months is recommended by the Centers for Disease Control, CDC) after the cessation of other immunosuppressive drugs such as azothioprine, cyclophosphamide and methotrexate, and in travellers being treated with immunosuppressive chemotherapy or radiotherapy for malignant disease. UK recommendations are that live vaccines are also contraindicated in travellers for 3 months after the cessation of high-dose (2 mg/kg or ≥40 mg per day for ≥7 days, or 1 mg/kg/day for 1 month) oral or rectal corticosteroids for conditions other than adrenal insufficiency. CDC recommends greater than or equal to 20 mg per day of prednisone or equivalent in people who weigh >10 kg, when administered for greater than or equal to 2 weeks and in this case waiting ≥1 month after discontinuation of high-dose systemic corticosteroids [2, 4]. Expert advice should be sought when considering the administration of live vaccines in travellers with what may be considered minor immunodeficiencies or who are receiving immunomodulating drugs such as interferon [2].

Travellers with HIV infection form a special group of immunocompromised travellers. BCG vaccine is contraindicated due to the risk of dissemination, and inactivated intramuscular typhoid and polio vaccines should be used instead of live oral typhoid and polio vaccines [1, 10]. Where possible, yellow fever vaccine should also be avoided due to the risk of myeloencephalitis in severely immunosuppressed individuals [2, 11]. Travel to yellow fever-endemic areas should be avoided or where unavoidable, strict protection against mosquito bites ensured. A medical letter of exemption should be issued for travel to regions where a yellow

fever vaccination certificate is required and vaccination is contraindicated. Following a careful risk assessment, yellow fever vaccine may be considered for those travellers with asymptomatic HIV infection with a CD4 count of 200–500/mm^3. There is no significant immunological risk and therefore no contraindication to the administration of yellow fever vaccine for those whose CD4 count is >500/mm^3 [2, 12]. The immunological response to vaccines may be suboptimal in travellers with HIV infection with rapid loss of antibody protection. Vaccination stimulates CD4 lymphocytes, which may lead to a temporary rise in HIV viral load; these travellers should ideally be receiving antiretroviral treatment and have undetectable viral loads in advance of vaccination [13–16]. It is particularly important to ensure travellers with HIV have been immunised with MMR, varicella, pneumococcal and influenza vaccines [1, 2].

Pregnancy and breast-feeding

With the exception of smallpox vaccine and perhaps yellow fever vaccine, there is no evidence that live or inactivated vaccines are harmful during pregnancy to the fetus or mother. However, where possible, it is recommended that vaccines should be deferred until after completion of pregnancy. Where indicated, inactivated and toxoid vaccines may be administered during pregnancy where there is a significant risk of infection [3]. Live vaccines are generally contraindicated in pregnancy and in women likely to become pregnant within the first 3 months after immunisation due to a theoretical risk of fetal infection and teratogenic effects on the fetus. Although pregnant women should be advised against travel to a yellow fever endemic region, yellow fever vaccination may be considered in the third trimester where the risk of yellow fever exposure is greater than the theoretical risk of the vaccine to the fetus. Termination of pregnancy following inadvertent immunisation is not advised since there is no evidence that live vaccines are teratogenic [2, 3]. Management with human normal immunoglobulin and human varicella immunoglobulin should be considered for non-immune pregnant women exposed to measles or varicella respectively [2].

Breast-feeding is not an absolute contraindication to vaccination with live or inactivated vaccines, though detailed discussions with breast-feeding travellers is recommended with regard to yellow fever vaccine administration [3].

Administration of vaccines

Healthcare professionals undertaking immunisation are accountable professionally as defined by their registration bodies and must be trained appropriately, including a review of their knowledge and skills on a regular basis. An anaphylaxis management kit containing intramuscular 1:1,000 adrenaline should always be available [2, 17–20].

Pre-vaccination serological testing is only necessary where there has been an adverse reaction to a previous dose of the vaccine, such as idiopathic thrombocytopenia purpura (ITP) post-MMR vaccination, and prior to BCG vaccination with respect to skin testing. It may also be part of a more cost-effective approach when prior natural immunity is uncertain, such as with hepatitis A and varicella.

It is important to read carefully the manufacturer's Summaries of Product Characteristics (SPCs) for each specific vaccine, which gives detailed information on the vaccine's storage, composition, reconstitution and preparation, colour and consistency, life span for use once drawn up, administration, side effects and contraindications [21]. Different vaccines should not be mixed in the same syringe [2, 3]

Some vaccines are supplied pre-prepared and ready for administration. Other vaccines are supplied lyophilised (freeze-dried) and must be reconstituted with the supplied dilutant before administration. A 21 G (green) needle is usually recommended for drawing up the dilutant and mixing it slowly with the lyophilised vaccine to avoid frothing [2]. Reconstituted vaccine and opened single or multi-dose vaccine vials must be used within the manufacturer's recommended period (usually within 1–4 h). Some multi-dose vials maybe used for up to 30 days if immediately stored in the refrigerator after use unless otherwise recommended by the manufacturer [7].

Correct administration of vaccines

Administration of a travel vaccine relies on the healthcare professional having:

- obtained patient consent
- ensured there are no contraindications to vaccination
- prepared the vaccine correctly
- reconstituted the product where necessary
- used the appropriate needle length for the size of the patient
- selected the correct site and route of administration and demonstrated an appropriate technique.

Post-vaccination management of the site, observation of the patient and documentation of the process are also vital.

Box 14.1 includes some guidance regarding best practice in vaccine administration.

Administration technique

It is important in terms of safety, immunogenicity and protective efficacy for the recommended dosage of a vaccine to be given by the approved route of administration at the recommended site. Localised reactions are more common when intramuscular vaccines are inadvertently administered

Box 14.1

- Travel vaccines are usually administered intramuscularly (IM), with a few exceptions and usually into either the deltoid area of the upper arm, or anterolateral aspect of the thigh. The Summary of Product Characteristics should be checked for the individual product to ensure correct site administration
- The deep subcutaneous (SC) route is usually preferred for individuals with bleeding disorders
- Intradermal route of administration is only used for BCG vaccination and as an alternative form of administration for rabies vaccine and such technique is specialised, requiring the healthcare professional receives appropriate training and assessment before such administration is undertaken
- Immunisations should not be given into the buttock, to avoid poor antibody response and sciatic nerve damage
- Skin cleansing is not required unless visible dirt is present, in which case soap and water can be used to clean the area
- A 25 mm needle is preferable and suitable for all ages, but consider a longer needle in those individuals of larger body mass index
- IM injections should be given with the needle at a 90° angle to the skin which should be stretched rather than bunched
- Deep SC injections should be given with the needle at a 45° angle to the skin which should be bunched rather than stretched
- There is no need to aspirate the syringe after the needle is introduced into the muscle
- Latex proteins may be found in some pre-filled syringes, in the tip cap and/or rubber plunger, and in the stoppers of some vaccines supplied in vials. If an individual has a history of severe (anaphylactic) allergy to latex then vaccines supplied in vials or syringes that contain latex should not be administered and a risk benefit analysis should be undertaken
- Vaccination should not be undertaken in the arm of a person who has undergone surgery for axillary lymph node dissection, particularly if, for example, extensive breast or lymph node surgery are performed for breast cancer, as this limb would be 'at risk' for lymphoedema
- The recipient of any vaccine needs to be observed for immediate adverse drug reactions (ADRs). However, there is no evidence to support the practice of keeping patients in the clinic post vaccination if there are no problems
- The vaccine name, product name, batch number and expiry date, dose, site of administration, date and name of vaccinator must be recorded

subcutaneously and thus most vaccines are given by intramuscular injection [22]. Generally, vaccines with an adjuvant are given intramuscularly to reduce the risk of localised irritation and granuloma formation [4]. Some vaccines are given by subcutaneous or intradermal injection. Patients with bleeding disorders (e.g. haemophilia) should also have intramuscular vaccines given by the deep subcutaneous route to reduce the risk of bleeding.

Intramuscular and subcutaneous injection

Intramuscular and subcutaneous vaccines should be administered into the anterolateral aspect of the thigh of infants and children less than 2 years old, and into the deltoid region of the upper arms in adults and older children to avoid large blood vessels and nerves. Vaccines are not administered into the buttock, where there is a risk of damage to the sciatic nerve, particularly at a site other than the upper outer quadrant. There is also an increased likelihood of injecting the vaccine into fatty tissue in the buttocks leading to reduced vaccine efficacy due to a lack of phagocytic or antigen-presenting cells in fat and increased enzyme denaturation of vaccine antigens. This is well illustrated with hepatitis B vaccines which are two to four times more likely to fail to reach a minimum antibody level of 10 mIU/l when injected into the buttock rather than into the arm [3, 23].

Intramuscular and subcutaneous vaccines should be administered with a 25 mm needle of either 23 G or 25 G. Very small infants may require a smaller 16 mm 25 G needle and likewise larger adults may require a longer 38 mm 21 G needle. Intramuscular vaccines are administered by stretching the skin at the site of injection between the thumb and forefinger and then inserting the needle at 90° to the skin into the muscle [3]. Subcutaneous vaccines are given by bunching (pinching) the skin together and then inserting the needle at 45° to the skin and into the subcutaneous tissue. It is not necessary to aspirate the syringe before injecting the vaccine, vaccines are never given intravenously, and one should ensure that all of the vaccine has been injected before withdrawing the needle to avoid tracking [2, 3].

Intradermal injection

Intradermal vaccines should be administered with a 26 G (10 mm) needle. The upper arm should be positioned at 45° to the body by resting their hand on their hip or holding the

Box 14.2 Further global resources for vaccine storage and vaccine administration

World Health Organization	WHO Immunization in Practice. A practical resource guide for health workers 2004 update http://www.who.int/vaccines-documents/DoxTrng/h4iip.htm
US	Centers for Disease Control and Prevention. Atkinson W, Wolfe S, Hamborsky J, McIntyre L (eds) (2011) *Epidemiology and Prevention of Vaccine-Preventable Diseases*, 12th edn. Public Health Foundation, Washington DC; http://www.cdc.gov/vaccines/Pubs/pinkbook/pink-appendx.htm
Australia	The Australian Immunization Handbook, 9th edn (2008); http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-home
Canada	Public Health Agency of Canada (2008) Immunization Competencies for Health Professionals; http://www.phac-aspc.gc.ca/im/pdf/ichp-cips-eng.pdf

Source: http://immunisation.dh.gov.uk/category/the-green-book/

arm extended in young children. The skin should be stretched between the thumb and forefinger of one hand and then the needle inserted almost parallel to the skin at a very slight angle with the bevel facing upwards about 2 mm into the superficial dermis so that one can see the needle just below the epidermis. The vaccine is then injected against the resistance of the dermis forming a bleb in the skin and a bleb of 7 mm diameter is approximately equivalent to 0.1 ml of vaccine administered. If there is no resistance during administration, the needle should be removed and reinserted before giving the remainder of the vaccine [2, 3]. The technique of intradermal vaccine administration is specialised, requiring that the healthcare professional receives appropriate training and assessment before such administration is undertaken.

BCG vaccine is always given by intradermal injection over the insertion of the left deltoid muscle, avoiding the tip of the shoulder, which predisposes to keloid scar formation. Some other vaccines may also be given intradermally, with intradermal rabies being one such vaccine, which requires less vaccine antigen per dose and is thus more cost-efficient and may be used on occasion. Intradermal vaccination induces a rapid macrophage-dependent T-lymphocyte response via specific epidermal cell; however, studies with intradermal hepatitis B vaccination have typically shown a relatively poor immune response compared with intramuscular vaccination [2, 3].

Paediatric and adult travel immunisations

There are a number of national and international organisations that publish travel immunisation guidelines. Guidelines may vary due to conflicting medical evidence, differing expert opinions, and different national licensing standards, marketing arrangements and availability of vaccines. This can cause confusion for both the traveller and the travel clinician [2, 3]. The recommended travel immunisations for an individual traveller will be determined by a detailed medical and travel consultation.

This section reviews in detail the current recommended paediatric and adult national guidelines of the UK for routine immunisations in the context of travellers, specific travel immunisations and mandatory travel immunisations. Reference is made to any major differences with the World Health Organization (WHO) international guidelines. The chapter concludes with two sections comparing the main differences between these guidelines and the national guidelines of the United States, Canada, Australia and New Zealand. The chapter thus aims to provide a comprehensive guide to travel immunisation for a travel clinician working in any part of the world.

Recommended UK paediatric and adult travel immunisation schedules

The WHO's International Travel and Health Book http://www.who.int/ith/en/ provides international travel immunisation guidelines that may be used by any country, including those that do not have their own national regulatory organisation and travel immunisation guidelines. Individual countries with their own travel immunisation guidelines may incorporate some but not all of the WHO guidelines where appropriate. The Department of Health in the UK publishes national travel immunisation guidelines in the Immunisation Against Infectious Disease Green Book www.dh.gov.uk/en/Publichealth/Healthprotection/Immunisation/Greenbook/DH_4097254 [1, 2].

Table 14.2 shows the recommended routine and travel specific immunisations in the UK. In Tables 14.2–14.4, the

Table 14.2 UK travel immunisation schedule

Vaccine	Routine recommended immunisation schedule (age)	Vaccine brand (s)	Route	Age (minimum age, catch-up schedules)	Dose	Primary schedule (recommended schedule expressed as time after first dose unless otherwise stated, accelerated schedule, and minimum intervals when different to recommended)	Booster (time after completion of primary schedule unless otherwise stated)
Routine vaccinations							
Hib	Routine: (2 m–<10 y) 3 doses (2 m (Pediacel); 3 m (Pediacel); 4 m (Pediacel)) Booster at 12 m (Menitorix)	Pediacel (DTaP/IPV/Hib) Menitorix (Hib/MenC)	IM	2 m–<10 y 2 m–<12 m ≥12 m	0.5 ml	3 doses (0, 1 m, 2 m) 3 doses (0, 1 m, 2 m) 1 dose (0)	Single booster of Menitorix (Hib/MenC) after 12 m of age only
HPV	Routine: (12 y–<18 y) 3 doses (12 y–13 y at time 0, 1–2 m, 6 m (with Cervarix))	Cervarix Gardasil	IM IM	10–<18 y 9–<18 y	0.5 ml	3 doses (0, 1-2 m, 6 m) OR 3 dose accelerated schedule (0, 1 m, 4 m) OR 3 dose accelerated schedule (0, 1 m, 2 m)	None
Influenza	Routine: (≥65 y) Annually (≥65 y)	New brands every 6 months depending on circulating strains of influenza	IM	6 m–<13 y ≥13 y	0.5 ml (0.25–0.5 ml for 6 m–<3 y)	2 doses (0, 4-6 w) 1 dose (0)	Annual
Measles, mumps and rubella (MMR)	Routine: (≥1 y) 2 doses (13 m; 3 y 4 m–5 y)	Priorix M-M-R II	IM	6–<12 m ≥12 m	0.5 ml	3 doses (0, after 12 m age, 1 m after 2nd dose) 2 doses (0, 1 m)	None

Meningococcal	Routine: (3 m–<25 y) 2 doses (3 m (MenC); 4 m (MenC)) Single booster at 12 m (Menitorix)	Meningococcal conjugate: Menitorix (Hib/MenC combined) Meningitec (monovalent) Menjugate (monovalent) NeisVac-C (monovalent)	IM	3–<12 m ≥12 m	0.5 ml	2 doses (0, 1 m) 1 dose (0)	Single booster at age 12 m None
Pneumococcal	Routine: (2 m–<2 y (PCV); ≥65 y (PPV)) 2 doses (2 m (PCV); 4 m (PCV)) Single booster at 13 m (PCV) Single dose ≥65 y (PPV)	PCV: Prevenar-13 PPV: Pneumovax II	IM	2–<12 m 1–<2 y ≥65 y	0.5 ml	2 doses (0, 2 m) 1 dose (0) 1 dose (0)	Single booster at age 13 m None None
Polio (IPV)	Routine: 3 doses (2 m (Pediacel); 3 m (Pediacel); 4 m (Pediacel)) Booster at 3 y 4 m–5 y (Repevax or Infanrix-IPV) Booster at 13–18 y (Revaxis) Then boosters every 10 y (Revaxis)	IPV: Pediacel ((DTaP/IPV/Hib) IPV: Revaxis (Td/IPV)	IM	2 m–<10 y ≥10 y	0.5 ml	3 doses (0, 1 m, 2 m)	1st Booster 1–3 y post primary schedule (with Repevax (dTaP/IPV) or Infanrix-IPV (DTaP/IPV) if <10 y (min. age 3 y 4 m); or with Revaxis (Td/IPV) if ≥10 y age). 2nd Booster 5–10 y after 1st booster (with Revaxis (Td/IPV)). Further boosters every 10 y (with Revaxis (Td/IPV)).

(*Continued*)

Table 14.2 (*Continued*)

Vaccine	Routine recommended immunisation schedule (age)	Vaccine brand (s)	Route	Age (minimum age, catch-up schedules)	Dose	Primary schedule (recommended schedule expressed as time after first dose unless otherwise stated, accelerated schedule, and minimum intervals when different to recommended)	Booster (time after completion of primary schedule unless otherwise stated)
Tetanus, diphtheria and pertussis	Routine: (≥2 m) 3 doses (2 m (Pediacel); 3 m (Pediacel); 4 m (Pediacel)) Booster at 3 y 4 m–5 y (Repevax or Infanrix-IPV) Booster at 13–18 y (Revaxis) Then boosters every 10 y (Revaxis)	Pediacel (DTaP/IPV/Hib); Repevax (dTaP/IPV); Infanrix-IPV (DTap/IPV) Revaxis (Td/IPV)	IM	2 m–<10 y ≥10 y	0.5 ml	3 doses (0, 1 m, 2 m)	1st Booster 1–3 y post primary schedule 2nd Booster 5–10 y after 1st booster Further boosters every 10 y
Travel Vaccinations:							
Anthrax	Not routine	HPA Anthrax Vaccine	IM	≥18 y	0.5 ml	4 doses (0, 3 w, 6 w, 6 m)	Annual
Cholera	Not routine	Dukoral	PO	2–<6 y ≥6 y	75 ml solution 150 ml solution	3 doses (0, 1–6 w, 1–6 w after 2nd dose) 2 doses (0, 1–6 w)	Every 6 m Every 2 y
Hepatitis A (monovalent)	Not routine	Havrix Monodose Havrix Junior Monodose Avaxim Vaqta Vaqta Paediatric Epaxal	IM IM IM IM IM IM	≥16 y 1–<16 y ≥16 y ≥18 y 1–<18 y ≥1 y	1.0 ml (1440 ELISA units) 0.5 ml (720 ELISA units) 0.5 ml (160 antigen units) 1.0 ml (50 antigen units) 0.5 ml (25 antigen units) 0.5 ml (500 RIA units)	1 dose (0)	Booster at 6-12 m, then every 20 y

Hepatitis B (monovalent)	Not routine	Engerix B	IM	0–<16 y	0.5 ml (10 µg)			3 doses (0, 1 m, 6 m) OR 4 doses (0, 1 m, 2 m, 12 m (booster))	Single booster at 5 y
				≥16 y	1.0 ml (20 µg)			3 doses (0, 1 m, 6 m) OR 4 doses (0, 1 m, 2 m, 12 m (booster)) OR 4 dose accelerated schedule (0, 7 d, 21 d, 12 m (booster))	
				11–<16 y	1.0 ml (20 µg)			2 doses (0, 6 m)	
		HBvaxPRO Paediatric		0–<16 y	0.5 ml (5 µg)			3 doses (0, 1 m, 6 m) OR 4 doses (0, 1 m, 2 m, 12 m (booster))	
		HBvaxPRO		≥16 y	1.0 ml (10 µg)			3 doses (0, 1 m, 6 m) OR 4 doses (0, 1 m, 2 m, 12 m (booster))	
		HBvaxPRO40		≥16 y	1.0 ml (40 µg)			3 doses (0, 1 m, 6 m)	
		Fendrix		≥15 y	0.5 ml (20 µg)			4 doses (0, 1 m, 2 m, 6 m)	
Hepatitis A & B (combined)	Not routine	Twinrix Adult	IM	≥16 y	Dose 1.0 ml	HAV 720 ELISA units	HBV 20µg	3 doses (0, 1 m, 6 m) OR 4 dose accelerated schedule (0, 7 d, 21 d, 12 m (booster))	Monovalent hepatitis A booster every 20 y. Monovalent Hepatitis B single booster dose at 5 y only.
		Twinrix Paediatric		1–<16 y	Dose 0.5 ml	HAV 360 ELISA units	HBV 10µg	3 doses (0, 1 m, 6 m)	
		Ambirix		1–<16 y	Dose 1.0 ml	HAV 720 ELISA units	HBV 20µg	2 doses (0, 6–12 m)	

(*Continued*)

Table 14.2 (*Continued*)

Vaccine	Routine recommended immunisation schedule (age)	Vaccine brand (s)	Route	Age (minimum age, catch-up schedules)	Dose			Primary schedule (recommended schedule expressed as time after first dose unless otherwise stated, accelerated schedule, and minimum intervals when different to recommended)	Booster (time after completion of primary schedule unless otherwise stated)
Hepatitis A & typhoid (combined)	Not routine	Hepatyrix	IM	≥15 y	Dose 1.0 ml	HAV 1440 ELISA units	Vi P Ty 25µg	1 dose (0)	Monovalent hepatitis A booster at 6–12 m, then every 20 y.
		ViATIM	IM	≥16 y	Dose 1.0 ml	HAV 160 antigen units	Vi P Ty 25 µg		Monovalent typhoid booster every 3 y.
Influenza A(H1N1)v	Not routine	Pandemrix	IM	6 m–<10 y ≥10 y	0.25 ml 0.5 ml			1 dose (0)	None
		Celvapan		≥6 m	0.5 ml			2 doses (0, 3 w)	
Japanese encephalitis	Not routine	Green Cross	SC	1–<3 y ≥3 y	0.5 ml 1.0 ml			3 doses (0, 7 d, 28 d) OR 2 dose accelerated schedule (0, 7–14 d) OR 3 dose accelerated schedule (0, 7 d, 14 d)	Green Cross: Additional Booster at 1 month for travelers > 60 y only Booster at 1 y Boosters then every 3 y
		IXIARO	IM	≥18 y	0.5 ml			2 doses (0, 28 d)	IXIARO: Under evaluation

Meningococcal	Not routine	Meningococcal quadrivalent (A, C, W135, Y) conjugate:	IM	3 m–12 m	0.5 ml	2 doses (0, 1 m)	Booster after 12 m
		Menveo		≥12 m		1 dose (0)	Under evalation
		Meningococcal quadrivalent (A, C, W135, Y) polysaccharide: ACWY Vax		≥5 y			Every 5 y for adults and children ≥5 y
Rabies	Not routine	Rab Rabipur	IM	≥1 m	1.0 ml	3 doses (0, 7 d, 28 d) OR 3 dose accelerated schedule (0, 7 d, 21 d)	Booster at 1 y, and then every 3-5 y
Tick-borne encephalitis	Not routine	TicoVac	IM	1–<16 y ≥16 y	0.25 ml 0.5 ml	2 doses (0, 4-12 w) OR 2 dose accelerated schedule (0, 2 w)	1st Booster at 5-12 m Further Boosters every 3 y
Tuberculosis	Not routine	BCG	ID	≤12 m >12 m	0.05 ml 0.1 ml	1 dose (0)	None
Typhoid	Not routine	Vi polysaccharide: Typhim Typherix	IM	≥2 y	0.5 ml	1 dose (0)	Every 3 y
		Ty21a: Vivotif	PO	≥6 y	1 capsule	3 doses (0, 2 d, 4 d)	Annual consisting of 3 doses (0, 2 d, 4 d) Every three years if living in endemic area
Varicella	Not routine	Varilrix Varivax	SC	1–<13 y	0.5 ml	1 dose (0)	None
				≥13 y	0.5 ml	2 doses (0, 4–8 w)	
Yellow fever	Not routine	Stamaril	SC	≥6 m	0.5 ml	1 dose (0)	Every 10 y

m = month, w = week, d = day, y = year

minimum age in the table does not apply for all listed vaccine brands and it is important to refer to each vaccine brand's Summary of Product Characteristics for the specific minimum age, licensed schedules, vaccine components and excipients, side effects and contraindications.

Immunisations

Anthrax

Indication Vaccination against anthrax should only be considered for adult travellers going to work with or handle infected animals or their products (such as wool, skin, bones and carcasses), for example farmers, veterinary surgeons, butchers, tanners and laboratory personnel. Anthrax is more common in Africa, Asia, Central and South America, and southern and eastern Europe [2].

Vaccine In the UK, the inactivated anthrax vaccine is manufactured by the Health Protection Agency (HPA Anthrax) [2]. Side effects may include localised pain, swelling and erythema (10%), headaches and myalgia (20%), fever (5%), nausea (5%) and anaphylaxis (< 1:100,000) [4].

Schedule The primary schedule for adults consists of four doses over a 6-month period, with the first dose administered at day 0, the second dose 3 weeks after the first dose, the third dose 3 weeks after the second dose and the fourth dose at least 6 months after the third dose, with annual boosters for travellers at continued risk of exposure [2, 3].

Efficacy Clinical trials with anthrax vaccines used in the 1950s and with Biothrax Anthrax vaccine indicate that the vaccines maybe more than 90% effective in preventing all types of anthrax infection for up to 1 year after completion of the primary schedule [4, 24].

Cholera

Indication The risk of cholera infection to travellers is extremely low and is estimated to be 1 in 500,000 travellers [25, 26]. Vaccination against cholera is only recommended for healthcare, humanitarian and laboratory personnel travelling to work in regions with a confirmed *Vibrio cholerae* serogroup 01 outbreak, such as refugee camps. It can also be considered for travellers to remote parts of Africa, Asia, the Indian subcontinent, and South and Central America where there is confirmed *V. cholerae* serogroup 01 and extremely limited healthcare resources [1, 2]. It is likely that due to surveillance difficulties and for fear of social and economic repercussions, morbidity and mortality data for *V. cholerae* are greatly underestimated [27]. However, strict food and water hygiene precautions remain the key to prevention of cholera infection in travellers. Cholera vaccination certification is no longer a WHO international health requirement for individuals travelling from infected areas, although an official document reiterating this fact may sometimes be helpful at some remote border areas [2, 28].

Vaccine In the UK and more than 60 countries, the oral inactivated whole-cell monovalent cholera vaccine Dukoral, prepared in a sodium hydrogen carbonate solution, is licensed for administration in travellers. It consists of four strains of *V. cholerae* serotype 01 representing the biotypes Classical and El Tor, and the subtypes Inaba and Ogawa of El Tor, with a recombinant cholera toxin subunit B but not the enterotoxin subunit A, which is responsible for the disease. Side effects can include mild gastrointestinal and flu-like symptoms [2, 3]. It does not provide protection against *V. cholerae* serotype 0139, which has started to spread through parts of South Asia, Southeast Asia and China. In Southeast Asia, two biovalent vaccines, Shanchol and mORCVAX, provide protection against both *V. cholerae* serotypes 01 and 0139 [28].

Schedule The primary schedule for travellers aged 2–6 years consists of three doses with boosters every 6 months. For older travellers the primary schedule consists of two doses with boosters thereafter every 2 years for ongoing protection. If longer than 6 weeks has elapsed between doses in the primary schedule or longer than the recommended interval for booster doses, it will be necessary to restart the primary schedule from the beginning [2, 28].

Efficacy The vaccination schedule should be completed at least 1 week and preferably 3 weeks before travel or potential exposure to *V. cholerae* 01 [1]. Studies suggest that the vaccine provides between 50% and 86% protection against *V. cholerae* 01 for up to 3 years [3, 25, 27, 29–33]. This protection can wane quickly, within 6 months in young children [3, 33].

The cholera toxin subunit B is antigenically similar to the heat-labile toxin of Enterotoxigenic *Escherichia coli* (ETEC). Dukoral thus also provides 50–67% cross-protection against ETEC infection, a more common cause of travellers' diarrhoea [7, 32, 34, 35]. Shanchol and mORCVAX do not contain cholera toxin subunit B and so do not provide cross-protection against ETEC [27].

Hepatitis A

Indication The incidence of hepatitis A infection is approximately 1.4 million cases per annum worldwide and it is one of the most common vaccine-preventable diseases in travellers [36, 37]. Hepatitis A vaccination is recommended for

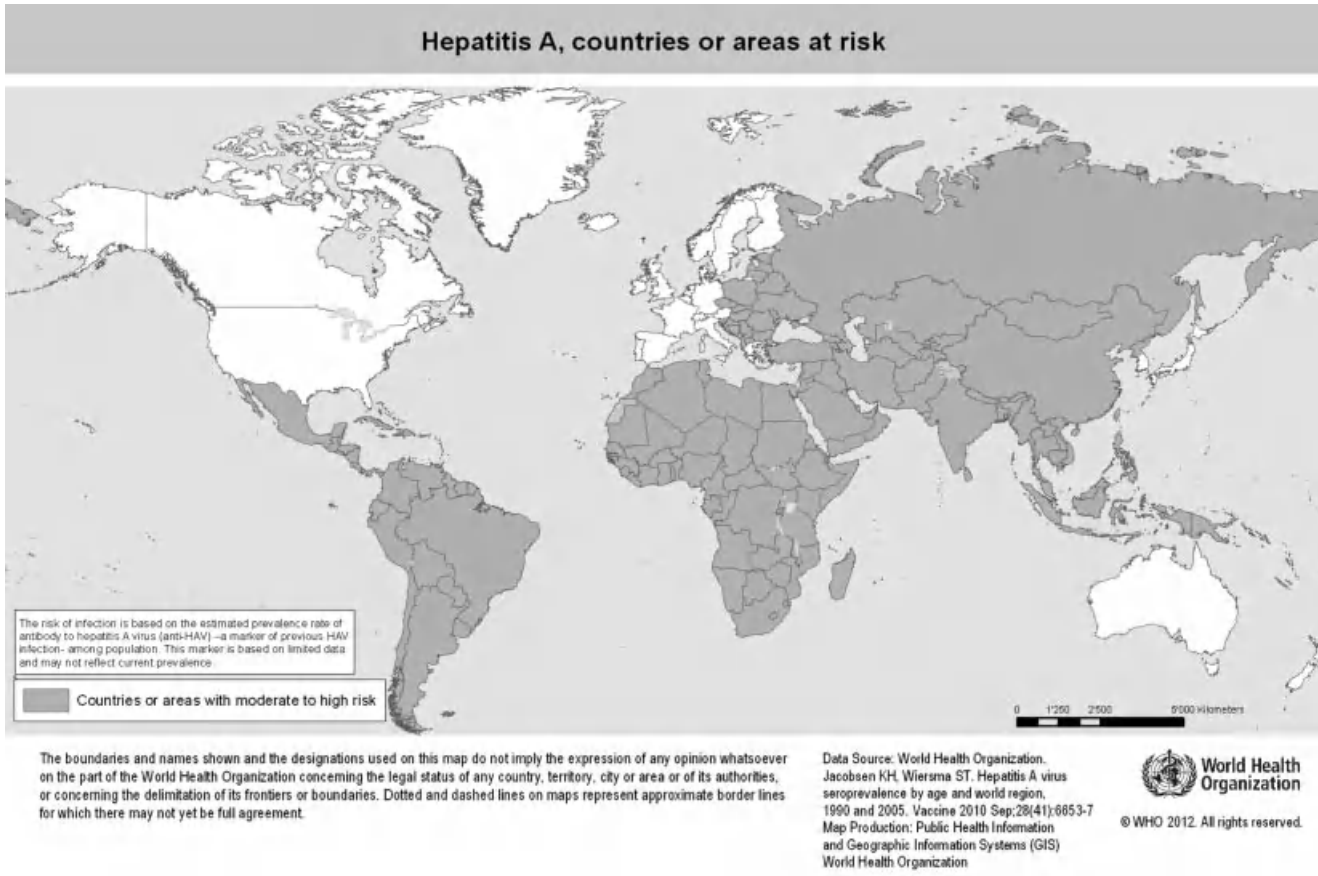

Figure 14.1 Hepatitis A, countries or areas at risk.

travellers aged >1 year to regions of intermediate to high prevalence of hepatitis A for prolonged periods, especially if food hygiene and sanitation is poor. This includes travel to most regions outside western and northern Europe, Canada, the US, Japan, Australia and New Zealand, but particularly to the Indian subcontinent and Southeast Asia [2, 38] (*see* Figure 14.1). Particular consideration with regard to the potential risk of exposure to infection with hepatitis A include travellers with underlying medical conditions, such as those with chronic renal or chronic liver disease including chronic hepatitis B or C, who may be at increased risk of severe hepatitis A infection [2]. It is recommended that a pre-vaccination IgG hepatitis A serology test is undertaken for those travellers born before 1945 or who are over the age of 40 and have lived in a hepatitis A-endemic area or have a history of jaundice, as they may have natural immunity to hepatitis A and not require hepatitis A vaccination [1]. Although the risk of hepatitis A infection in infants and young children who travel may be low, with subclinical infection occurring mostly, severe infection can occur with transmission to others. Hepatitis A vaccines combined with hepatitis B or typhoid vaccines can be used when protection against both of these infections is recommended [2].

Vaccine Several inactivated monovalent hepatitis A vaccines are licensed in the UK, including a hepatitis A and B combined vaccine and hepatitis A and typhoid combined vaccines [2]. Combined hepatitis A and B vaccines consist of inactivated hepatitis A virus combined with recombinant hepatitis B surface antigen, together with an aluminium salt adjuvant [2]. Combined hepatitis A and typhoid vaccines consist of inactivated hepatitis A virus combined with inactivated purified Vi capsular polysaccharide typhoid vaccine and an aluminium hydroxide adjuvant [2]. Hepatitis A vaccines are very safe and well tolerated, with the more common side effects including localised pain and headache. The monovalent hepatitis A vaccine Epaxal contains influenza virus haemagglutinin and is thus contraindicated in travellers who are allergic to eggs or chicken protein [2].

Schedule The primary immunisation schedule for hepatitis A depends on the type administered, age of the traveller and

whether combined protection with hepatitis B or typhoid is required. Some of the different hepatitis A vaccines contain different concentrations of antigen as shown in Table 14.2, and although the different vaccines may be used interchangeably during courses and for boosters, this is only to be recommended when the original vaccine used is unavailable [2].

The primary schedule for the monovalent hepatitis A vaccines for travellers greater than 1 year of age includes the administration of a single dose on day 0 with a booster dose at 6–12 months. National guidelines in the UK currently recommend further boosters every 20 years, although the WHO does not recommend any further boosters after that at 6–12 months [1, 2, 39].

The primary immunisation schedule for the combined hepatitis A and B vaccine consists of three doses for Twinrix Adult and Twinrix Paediatric over a 6-month period. An accelerated schedule over 3 weeks with Twinrix Adult provides rapid protection against hepatitis A and B. The primary immunisation schedule for travellers aged 1–15 years with Ambirix consists of just two doses, on day 0 and at 6–12 months as it contains double the concentration of both hepatitis A and B antigens as contained in Twinrix Paediatric. The first dose of Ambirix provides sufficient protection against hepatitis A and the second dose is required to provide sufficient protection against hepatitis B. Monovalent hepatitis A vaccines or Ambirix (for children less than 15 years old) are recommended when rapid single-dose protection against hepatitis A is required, rather than Twinrix Paediatric or Twinrix Adult. Booster doses with monovalent hepatitis A and monovalent hepatitis B vaccines are then recommended after completing the primary schedule with a combined hepatitis A and B vaccine [2]. The primary immunisation schedule for the combined hepatitis A and typhoid vaccines for travellers aged >15 years includes the administration of a single dose of the combination vaccine followed by booster doses of monovalent hepatitis A and monovalent typhoid vaccine as appropriate for ongoing protection [2].

Efficacy A single dose of hepatitis A vaccine provides at least 95% protection for up to 1 year. The booster dose at 6–12 months provides nearly 100% protection for at least 25 years and probably for life [1, 3, 39–42]. The combined Twinrix Paediatric or Twinrix Adult vaccines administered as three doses, on day 0, 1 month and 6 months, provide after each respective dose 94%, 99% and 100% protection against hepatitis A, and 71%, 97% and 99% protection against hepatitis B [3, 43–46]. The accelerated schedule with Twinrix Adult on day 0, 7, 21 and at 12 months provides at 1 month, 12 months and 13 months 99%, 96% and 100% protection against hepatitis A, and 82%, 94% and 100% protection against hepatitis B respectively [47–50].

Human normal immunoglobulin (HNIG) is no longer recommended for administration as hepatitis A pre-exposure prophylaxis due to the extremely immunogenic properties of the hepatitis A vaccine and the relatively long incubation time of hepatitis A [2].

Post-exposure prophylaxis Unimmunised travellers exposed to a potential source of hepatitis A should receive a single dose of monovalent hepatitis A vaccine within 1 week of the onset of jaundice or other symptoms in the index case. If longer than 1 week has elapsed, such travellers should receive a dose of HNIG containing a hepatitis A antibody level >100 IU/ml. The dose of HNIG for travellers aged <10 years is 250 mg and >10 years 500 mg. HNIG provides 85% protection if administered within 2 weeks of exposure and it is likely to modify the severity of hepatitis A infection [37].

Hepatitis B

Indication It has been estimated that worldwide, 2 billion people are infected with hepatitis B with more than 350 million carriers of the disease [1]. The risk of infection to travellers has been estimated to be 80–240 cases per 100,000 travellers per month of stay for long-term travellers and 2–10 times lower among short-term travellers. Hepatitis B is an important vaccine-preventable disease in travellers [2, 51].

Hepatitis B vaccine is a routine childhood vaccination in more than 90 countries worldwide but currently is not part of the UK routine childhood immunisation programme. Hepatitis B vaccination is recommended for travellers to areas of intermediate (2–8%) to high (>8%) prevalence of hepatitis B as based on the local population hepatitis B surface antigen prevalence [1, 2]. This includes travel to sub-Saharan Africa, most of Asia and the Pacific, the Indian subcontinent, Middle East, the Amazon region of South America, Honduras, Guatemala, Haiti, Dominican Republic, and parts of eastern, central and southern Europe (*see* Figure 14.2). Travellers to these regions at particularly high risk include those who plan to remain in areas of high or intermediate prevalence for long periods of time; young children who may be in contact with other young children in an endemic area; children and others who may require medical care while travelling to visit families or relatives in high or moderate-endemicity countries; travellers with medical conditions who may require blood product transfusions, dialysis or other medical or dental treatment and who may be exposed to infection through unsterile injections or unscreened blood or blood products; travellers with chronic liver disease; and those travelling for medical care. Other indications include for those travellers who engage in lifestyle behaviours that may expose them to a risk of hepatitis B, including sexual activity, intravenous drug use, acupuncture, piercing,

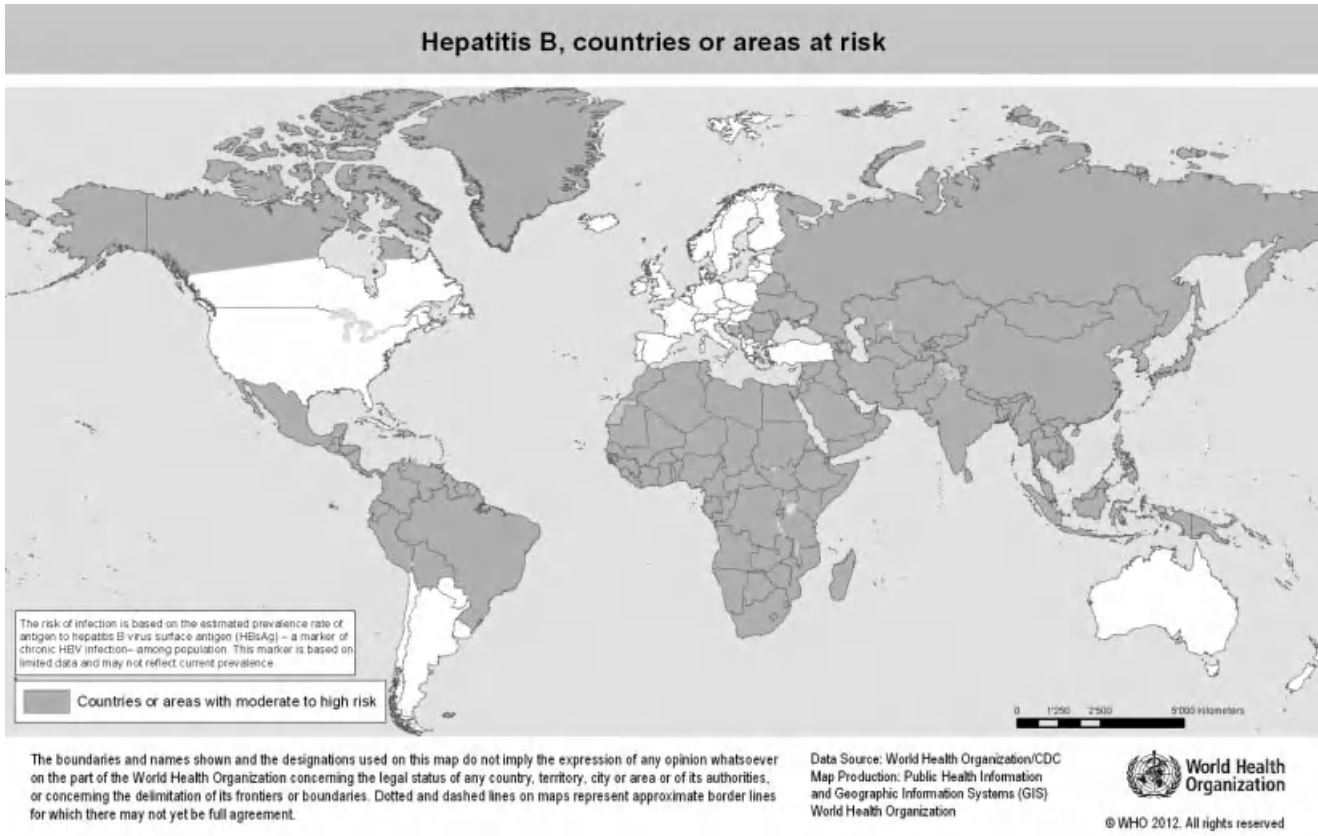

Figure 14.2 Hepatitis B, countries or areas at risk.

tattooing and participation in contact sports. Occupational exposure should also be considered for healthcare workers and laboratory personnel. Combined hepatitis A and B vaccines can be used when protection against both hepatitis A and hepatitis B infection is desired [2].

Vaccine Several inactivated monovalent hepatitis B vaccines are licensed for use, including a combined hepatitis A and B vaccine (see section on Hepatitis A vaccine) [2]. The vaccines are very safe with few experiencing mild side effects, including localised pain and a mild fever [2, 3].

Schedule The primary immunisation schedule for hepatitis B depends on the type of vaccine administered, the age of the traveller, how quickly protection is required and whether combined protection with hepatitis A is required. Different hepatitis B vaccines may contain different concentrations of antigen and although the different vaccines may be used interchangeably during courses and for boosters, this is only to be recommended when the original vaccine used is unavailable [2, 52].

The primary schedule of most monovalent hepatitis B vaccines consists of three doses administered over a 6-month period, at day 0, 1 month and 6 months. Some vaccines may also be given as a three-dose schedule over 2 months, at day 0, 1 and 2 months with a booster at 12 months [2, 53]. For travellers aged >18 years departing within 1 month, Engerix B may be administered according to an accelerated schedule over 3 weeks with a fourth booster dose administered at 12 months [2, 53–57] It can also be administered in those 16–18 years where it is important to provide rapid protection and to maximise compliance.

For travellers aged <16 years, Engerix B may be given as a 0.5 ml (10 µg) dose according to a three-dose accelerated schedule, at day 0, 1 and 6 months and for travellers aged 11–15 years, Engerix B may be administered as a 1.0 ml (20 µg) adult dose according to a two-dose schedule over 6 months when the risk of infection with hepatitis B is considered to be low and to aid compliance. Consideration should be given to the administration of a single booster dose of hepatitis B vaccine at 5 years for travellers at ongoing risk of hepatitis B infection [2].

Efficacy A complete course of hepatitis B immunisation is likely to be at least 80% effective in preventing infection. More than 80% of adult travellers develop adequate

antibody protection after two doses of hepatitis B vaccine (this is higher in younger children). Between 90% and 100% of travellers develop an adequate antibody response after three doses of hepatitis B vaccine [58–60]. Rates of protection are slightly lower in older travellers and in travellers with certain medical conditions, including immunosuppression, those requiring dialysis and those who are obese [3]. Although antibody levels decline over time, immunological memory and protection against hepatitis B infection persists for more than 20 years and probably for life [61].

The accelerated course of hepatitis B vaccine using Engerix B with three doses administered over 3 weeks provides 65% seroprotection within 1 week of completing the course and 98% within 1 month after the fourth booster dose at 12 months [50, 53]. This course of hepatitis B vaccine is to be recommended for those travelling imminently and when there is insufficient time to complete a three-dose course over a period of 6 months.

For infants and young children who have received a primary course of hepatitis B vaccine, a single booster of hepatitis B vaccine is recommended at 5 years of age, which provides protection for at least 15 years and probably for life, although there is much individual variability [1, 61]. Further booster doses of hepatitis B vaccine are not routinely recommended thereafter.

Non-response to hepatitis B vaccine occurs in approximately 10–15% of adult vaccinees and is associated with several factors, including incorrect administration, gender (male), age over 40 years, obesity, smoking, alcoholism, renal insufficiency and immunosuppression. Research into the mechanisms associated with non-response has demonstrated immunogenetic mechanisms, including specific haplotype associations [62]. Serological testing is recommended for the older traveller in order to demonstrate that protection has been afforded, travellers who are to be deployed as healthcare workers, for those with underlying medical conditions and those who may be at continued risk of exposure by virtue of travel. Such travellers may require additional booster doses of hepatitis B vaccine if they fail to mount an adequate antibody response, and the administration of a course of a combined hepatitis A and B vaccine may be considered as there is evidence to suggest that the combined hepatitis A and B vaccine may circumvent non-response to hepatitis B vaccine. Importantly, in the event of a potential exposure to infection with hepatitis B, consideration should be given to the administration of post-exposure prophylaxis in the form of hepatitis B immunoglobulin and booster doses of hepatitis B vaccine for non-responders and if hepatitis B surface antibody levels are <10mIU/mL [2].

Post-exposure prophylaxis Unimmunised travellers exposed to potential infection with hepatitis B should receive three doses of hepatitis B vaccine administered on day 0, 1 month and 2 months, with a booster at 12 months. If the risk of infection is considered significant, e.g. the source is confirmed as HBsAg positive, unimmunised travellers should also receive a dose of hepatitis B specific immunoglobulin (HBIG) preferably within 48 hours but up to 7 days following exposure. Immunised and partially immunised travellers should receive a booster dose of hepatitis B vaccine and complete the course as necessary [2, 3].

Human papillomavirus

Indication All female travellers aged 12–18 years should receive the human papillomavirus (HPV) vaccine. This includes females who are already sexually active, as they may not have been exposed to the high-risk HPV 16 and 18 types which the vaccine protects against. Although there is no evidence that HPV vaccination causes harm during pregnancy, it should generally be postponed until after pregnancy unless high-risk sexual activity is continuing during the pregnancy [2]. HPV vaccination is an opportunity to reduce the risk of acquiring HPV while travelling, particularly in young women travelling abroad during a gap year [3]. Consideration should be given to the administration of HPV vaccine to men who may be at risk of genital warts and HPV-related cancers.

Vaccine Cervarix is a bivalent HPV vaccine protecting against HPV types 16 and 18, which are associated with 50% and 15% respectively of cervical cancers [63]. Gardasil is a quadrivalent HPV vaccine protecting against HPV type 6, 11, 16 and 18 with HPV types 6 and 11 being associated with 90% of genital warts [64].

Schedule Cervarix is currently part of the routine immunisation schedule for adolescent girls in the UK and is administered at day 0, 1 month and 6 months [2]. Gardasil provides additional protection against genital warts and so may be preferential for some female adolescent travellers.

Efficacy Both vaccines are >99% effective in protecting women against pre-cancerous anogenital lesions associated with HPV 16 and 18 for at least 6 years and probably much longer [65]. The vaccines also provide some cross-protection against some other high-risk HPV types with similar structures. Gardasil provides 99% protection against genital warts associated with HPV types 6 and 11 [66]. Alongside vaccination, advice about safe sex should be given and the importance of attending routine cervical screening must also be stressed [2].

Influenza

Indication In the UK, influenza vaccination is recommended for travellers >6 months.[2, 4, 8, 67]

Vaccine Influenza is present year round in the tropics, peaks between November and March in the northern hemisphere, and between April and September in the southern hemisphere [2, 3]. The principal strains of influenza circulating in the northern and southern hemispheres may vary significantly from one other. The WHO monitors globally the seasonal antigenic drift and periodic antigenic shift in influenza A haemagglutinin (H) and neuraminidase (N) surface antigens. Antigenic drift is due to point mutations and antigenic shift is due to genetic recombination. Influenza B has less antigenic drift and influenza C is only responsible for a very small portion of clinical illness. Intramuscular inactivated influenza vaccines are trivalent and consist of two subtypes of influenza A (H3N2 and H1N1) and one subtype of influenza B [1, 2, 68]. There are three main types of influenza vaccine: split virion (whole virus strains), surface antigen and surface antigen virosomes [2, 57].

The WHO provides recommendations 6 months in advance of the annual influenza season occurring in each hemisphere regarding which virus strains should be included in the influenza vaccines for the forthcoming winter season. In years when the strains of influenza in the northern and southern hemispheres are different, the influenza vaccines available in each hemisphere will also be different. Those travelling from one hemisphere to the other during that hemisphere's influenza season should be vaccinated at least 2 weeks before departure, with an influenza vaccine specific for that hemisphere. If such an influenza vaccine is not available before travel, the traveller should be vaccinated with an influenza vaccine specific to that hemisphere as soon as possible after arriving in a country within that hemisphere [1, 3].

All three different types of influenza vaccine have similar side effects, which may include mild flu-like symptoms and very rarely neuralgia, paraesthesiae, seizures, vasculitis, thrombocytopenia, neuritis and encephalomyelitis. There is a possible association with Guillain-Barre Syndrome of <1 per million doses. Split virion vaccines are slightly less reactogenic and are preferred in younger children, and influenza vaccine is contraindicated in travellers with a previous anaphylactic reaction to the vaccine or to egg products [2].

Schedule The primary immunisation schedule for children aged 6 months to 13 years and for all immunocompromised children and adults includes two doses, administered on day 0 and at 4–6 weeks. For immunocompetent adults and children aged >13 years, the primary schedule consists of a single dose only. Annual single dose boosters for all ages are then recommended for ongoing protection due to the antigenic drift and shift of influenza A. Influenza vaccine in the UK is normally administered between September and November, just before the start of the flu season.

Efficacy All of the different types of influenza vaccine provide a similar protection of 70–80% against infection with influenza strains contained within the vaccine for up to 1 year [69, 70]. They are much less effective in travellers aged >65 years in whom they may provide protection for only 4 months, although at present booster doses within the same year are not recommended [14, 71].

Influenza A(H1N1)v

Indication Influenza A(H1N1)v vaccination is currently recommended for travellers aged >6 months who are at increased risk of influenza A(H1N1)v or severe illness. This includes healthcare workers, pregnant women, children with neurodevelopmental disorders and travellers with chronic medical conditions such as diabetes, chronic pulmonary disease, immunosuppression, asplenia or splenic dysfunction among others [2, 72]. Vaccination is not currently routinely recommended in travellers aged >65 years as they seem to have some immunity to influenza A(H1N1) virus due to exposure to similar viruses in the past [73].

Vaccine Influenza pandemics occur when a new influenza virus emerges and spreads through a population in which there is little or no immunity. There have been three pandemics in the previous century and they have tended to be associated with high mortality as individuals have little or no immunity to the emerging virus. The most recent influenza pandemic began in 2009 and was associated with A(H1N1)v 2009 virus (swine flu). This new influenza subtype consisted of gene segments from human influenza A, pigs and bird viruses. There have also been sporadic outbreaks of avian influenza caused by the avian influenza A(H5N1) virus particularly in some countries in Southeast Asia. Inactivated H5N1 vaccines are available in some countries, although they are not generally available and their effectiveness is not known [1].

The side effects are likely to be similar to those experienced with seasonal influenza vaccine. Pandemrix is contraindicated in travellers with a previous anaphylactic reaction to egg products, but Celvapan is propagated in Vero cells and so may be administered as an alternative [2]. A swine flu vaccine used in 1976 in the US was associated with a very slight increase in the risk of Guillain-Barré Syndrome (GBS) [74]. However, there is no evidence to suggest that the

current influenza A(H1N1)v vaccines are associated with an increased risk of GBS.

Schedule Pandemrix is the preferred vaccine for children and pregnant women as it provides rapid protection following administration of a single dose, and there are limited data on the use of Celvapan in children. The primary schedule with Celvapan is the administration of two doses, separated by an interval of at least 3 weeks, while Pandemrix is administered as a single dose. The two vaccines are not interchangeable [2].

Japanese encephalitis

Indication This risk of infection with Japanese encephalitis for travellers to endemic countries is very low, <1 per million travellers, rising to 1 per 5,000 per month for the local population in endemic rural areas [3]. Japanese encephalitis is endemic in the tropical regions of Southeast Asia, southern India and Sri Lanka (*see* Figure 14.3), occurring throughout the year and especially during their rainy seasons. In the more subtropical regions of northern Southeast Asia, northern India and Nepal, Japanese encephalitis typically occurs in epidemics during the rainy season from April to October [1, 2]. Japanese encephalitis vaccination is recommended for travel to endemic areas of the Indian subcontinent, Southeast Asia and the Western Pacific for longer than 1 month [2, 3]. However, cases do occur in travellers to endemic regions for shorter durations [75]. Vaccination is also recommended for travel of any duration to endemic areas during and just after the rainy season, and to rural areas where rice and pig farming coexist. Japanese encephalitis is not found in Africa, the Americas or Europe [2, 76].

Vaccine Two Japanese encephalitis vaccines are available in the UK: Japanese encephalitis Green Cross vaccine (GC vaccine) is currently unlicensed in the UK and is supplied on a named patient basis, and IXIARO. JE-VAX (Biken) is an inactivated vaccine derived from mouse brain cells and is no longer manufactured or available [2, 21, 77].

Green Cross vaccine is highly reactogenic and contains inactivated Japanese encephalitis virus cultured in mouse brain cells. It should be administered at least 10 days prior to departure to monitor for potential side effects, which

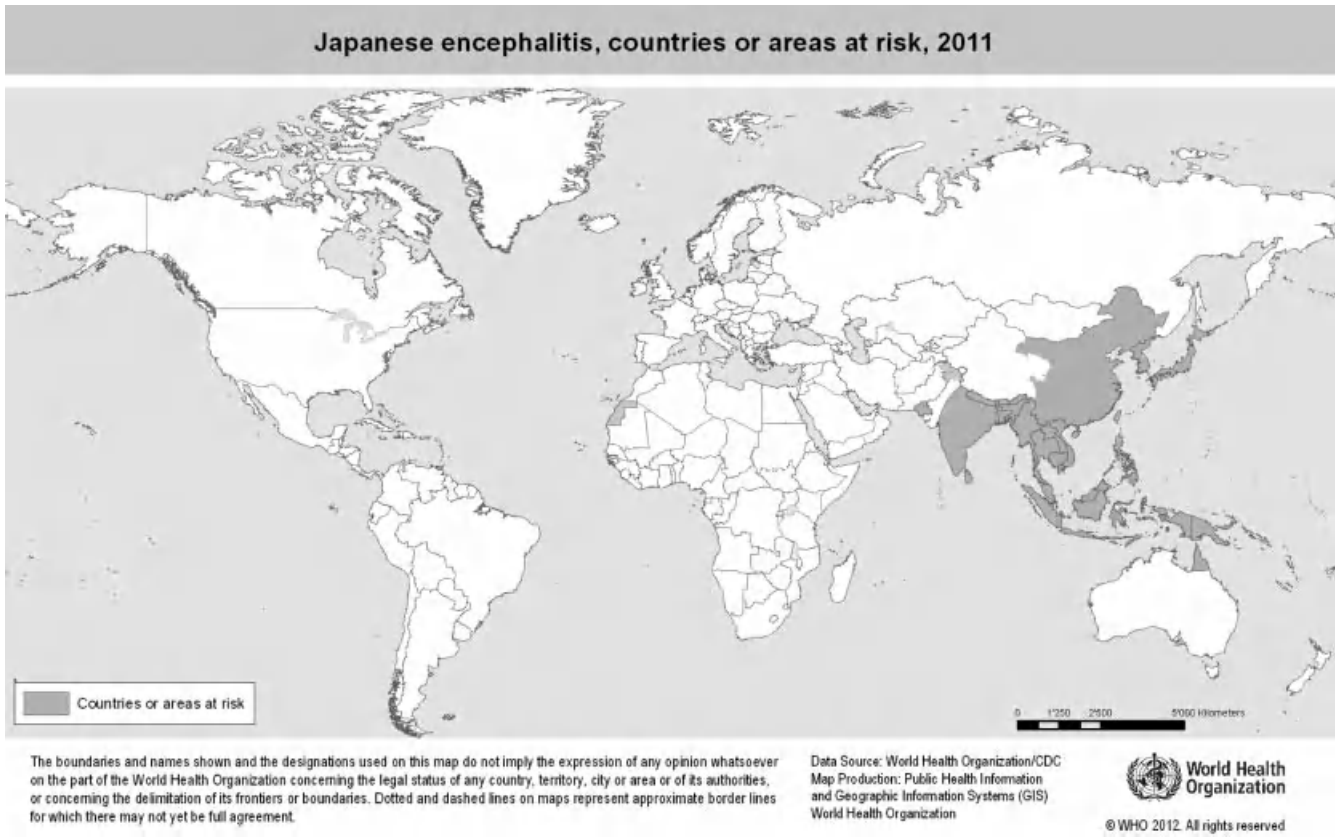

Figure 14.3 Japanese encephalitis, countries or areas at risk, 2011.

include fever, headache, myalgia, abdominal pain, vomiting, dizziness, angioedema and, very rarely, severe neurological side effects [2, 3]. IXIARO is manufactured from Japanese encephalitis virus produced from Vero cells and the main side effects are myalgia and headache [2, 21, 77]. Japanese encephalitis vaccination is not recommended in travellers with unstable neurological conditions, including those who have had convulsions in the previous year or who have conditions such as multiple sclerosis [2].

Schedule The primary immunisation schedule for Green Cross vaccine consists of three doses administered over 1 month to those aged 1 year and over. An accelerated schedule for travellers leaving imminently consists of two or three doses administered over a 2-week period. An additional booster dose is recommended 1 month after completing the primary course for travellers aged >60 years and a booster dose is then recommended at 1 year with further boosters every 3 years [2].

The primary immunisation schedule for IXIARO vaccine for travellers consists of two doses administered over 1 month for those aged 18 years and over (IXIARO is the only Japanese encephalitis vaccine available in North America and is only licensed for persons aged >17 years). The need for booster doses is currently under evaluation. There no evidence for the interchangeability of different vaccines during a schedule and so at present this is not recommended [2].

Efficacy The rate of seroconversion following administration of the first dose of IXIARO is approximately 30% rising to 97% 1 week after the second dose and completion of the primary schedule [8, 78]. The duration of protection provided with IXIARO is currently unknown and under evaluation [77]. The protective efficacy of the Green Cross vaccine is approximately 80% after completion of the primary schedule [3].

Measles, mumps and rubella

Indication MMR vaccination is part of the UK routine childhood immunisation programme. Measles, mumps and rubella are more common in many developing countries, especially where routine childhood immunisation programmes are not in place or where vaccination coverage is low. All travellers aged >6 months to countries where measles, mumps and/or rubella are endemic should be vaccinated with MMR. Children aged <6 months are likely to be protected by maternal antibody [3]. Travellers from the UK born before 1970 may be considered naturally immune to measles, mumps and rubella due to the high incidence of natural exposure before this time, although they may wish to be immunised on request. Older travellers who have received inactivated monovalent measles vaccine may paradoxically be at risk of more severe measles infection due to sensitisation to measles antigen and so should be revaccinated with MMR [2]. It is particularly important that women travellers of childbearing age have been vaccinated with MMR or have serological evidence of rubella antibodies [2].

Vaccine In the UK, MMR vaccines are only available in combination, consisting of live strains of measles, mumps and rubella attenuated viruses [2]. A common side effect (3%) occurring 1 week post-vaccination is a rash, fever and malaise lasting for 2–3 days. Rarely this may be associated with febrile convulsions, although the risk is higher with natural measles infection. A transient arthralgia may occur 1–3 weeks post vaccination especially in post-pubertal women (25%) due to the rubella component of the vaccine. Parotid swelling may occur typically in the third week. Rarely (1 per 32,000 doses), idiopathic thrombocytopenic purpura (ITP) may occur within 6 weeks of vaccination, which spontaneously resolves. This risk is much less than the risk of ITP associated with wild measles or rubella virus infection [79]. If ITP occurs within 6 weeks after the first dose of MMR, serological testing should be performed and the second dose of MMR only administered if there is incomplete seroconversion to measles, mumps and rubella. MMR is contraindicated in pregnant women and immuocompromised travellers and it should only be administered, and with extreme caution, in a hospital setting to travellers with a previous severe allergic reaction to egg products. There is overwhelming evidence that MMR is not associated with an increased risk of autism, inflammatory bowel disorders and Guillain-Barré Syndrome as some studies have suggested in the past [2, 80, 81].

Schedule MMR is recommended when protection against measles, mumps and/or rubella is required. The primary immunisation schedule consists of two doses administered 4 weeks apart after 12 months of age. Maternal antibodies may persist and inhibit the MMR vaccine up to 18 months of age, leading to the primary failure of the immune response to the first MMR dose. Therefore, any dose administered before 12 months of age should effectively be discounted and the second dose in the schedule should ideally be administered after 18 months of age [2, 82].

Travellers born before 1996 when the two-dose MMR schedule was introduced, may incorrectly believe they are adequately immunised, but they may have had only a single dose of MMR (available since 1988), MR (used in a catch-up programme in 1994), monovalent measles vaccine (available from 1968) or monovalent rubella vaccine (available from 1970) [2].

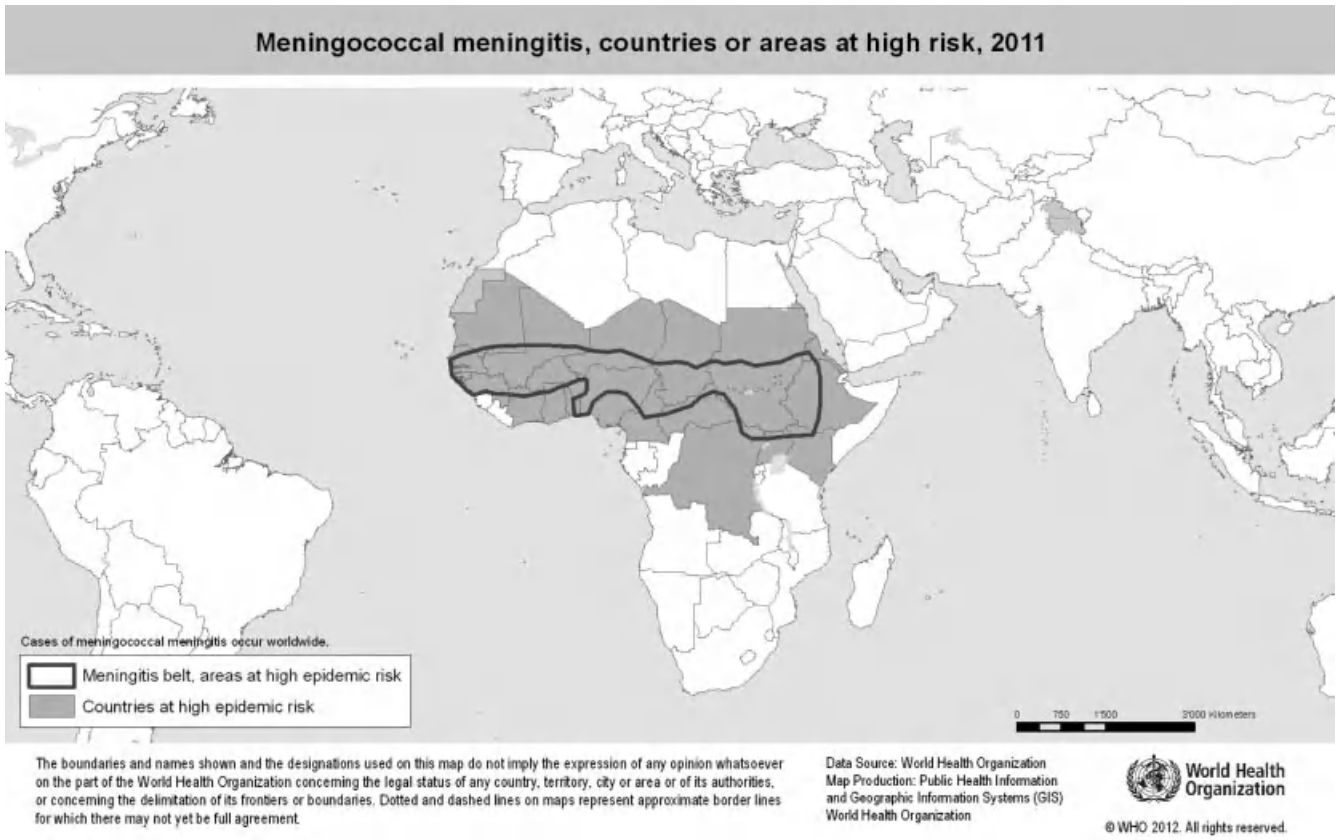

Figure 14.4 Meningococcal meningitis, countries or areas at high risk, 2011.

Efficacy A single dose of MMR provides approximately 90% protection against measles, 61–91% protection against mumps and 95–100% protection against rubella [3, 83, 84]. A second dose of MMR targets those individuals who may not have seroconverted following the first dose of MMR, and approximately 90% of travellers who do not respond to the first dose of MMR should respond to the second dose [2].

Post-exposure prophylaxis Unimmunised or partially immunised travellers >6 months of age exposed to measles may be offered a dose of MMR vaccine, ideally within 3 days of the exposure as vaccine-induced measles antibody develops faster than that following natural infection. A dose of HNIG should be considered for travellers who are immunocompromised, pregnant and unimmunised on serological testing, or aged <9 months within 6 days of exposure to a confirmed or highly suspected case of measles [2].

Meningococcal meningitis

Indication In the UK, meningococcal serogroups B and C are the most common cause of meningococcal infection [2]. All travellers aged 3 months to 25 years should be up to date with the routine meningococcal C conjugate vaccine immunisation schedule. Vaccination is also recommended for all unvaccinated individuals studying at school or university in the UK. Meningococcal C conjugate vaccination is recommended for all travellers aged >3 months with asplenia or splenic dysfunction because they are at increased risk from meningococcal infection [2].

Meningococcal disease occurs worldwide (*see* Figure 14.4), with certain serogroups being more prevalent in some regions. The meningococcal quadrivalent vaccine is the preferred vaccine for travellers as it provides protection against serogroups A, C, W135 and Y. It is recommended for travellers aged >3 months to regions where meningococcal serogroups A, W135 or Y are circulating and where epidemics are prevalent. Epidemics of meningococcal serogroups A and W135 occur during the annual Hajj pilgrimage to Mecca in Saudi Arabia and meningococcal quadrivalent vaccination is a mandatory visa entry requirement for Hajj and Umrah. Quadrivalent vaccination is also recommended for travel to the meningitis belt of sub-Saharan Africa during the dry season (December–June), when significant epidemics of

meningococcal serogroup A (and more recently serogroup W135 as well) occur. This is particularly important for backpackers and travellers going to live or work in close proximity within local communities for long periods of time during the dry season [3, 85]. Quadrivalent vaccination is recommended for all travellers going to study at institutions abroad and may constitute a mandatory entry requirement in order to study at universities in the United States [2].

Vaccine Three types of inactivated meningococcal vaccine are licensed in the UK: the routine childhood MenC conjugate vaccine, the meningococcal quadrivalent (A, C, W135 and Y) polysaccharide vaccine and the meningococcal quadrivalent (A, C, W135 and Y) conjugate vaccine (Menveo) for travellers [2].

For many years the only available quadrivalent meningococcal travel vaccine in the UK was a capsular polysaccharide vaccine (ACWY Vax), which as a T cell-independent vaccine is both poorly immunogenic in children aged <2 years and provides a relatively shorter duration of protection. The conjugate meningococcal quadrivalent travel vaccine has been available in Europe and the UK (Menveo) since March 2010, with the most common side effects being localised pain, swelling, erythema, mild fever, headaches, myalgia and nausea [2, 21].

Schedule The meningococcal quadrivalent conjugate vaccine is licensed and recommended for travellers aged ≥11 years old. In April 2010, the Joint Committee on Vaccines and Immunisation of the Department of Health, UK, recommended that conjugate ACWY meningococcal vaccine should be used in preference to the polysaccharide ACWY meningococcal vaccine, as the conjugated quadrivalent vaccine is more immunogenic and less likely to be associated with hyporesponsiveness. The conjugated ACWY vaccine may be administered as two doses separated by one month in infants under one year with a single booster dose after 12 months of age. For children over 1 year of age and adults, a single dose may be administered. The meningococcal quadrivalent polysaccharide vaccine is no longer recommended in infants and young children but may be used in travellers aged ≥5 years old. Where an infant has already received the monovalent MenC conjugate vaccine previously and meningococcal quadrivalent conjugate vaccine is indicated because of travel, it is recommended than an interval of 2 weeks is observed before administration of the conjugate quadrivalent vaccine [2].

Efficacy The meningococcal quadrivalent polysaccharide vaccine is more than 80% effective in providing short-term (<3 years) protection against meningococcal serogroups A, C, W135 and Y in travellers aged >3 months [2, 21]. In travellers aged <2 years it is only sufficiently immunogenic for the polysaccharide serogroup A and protection quickly wanes [86]. Studies suggest that Menveo is at least as immunogenic and in some cases more immunogenic against all four meningococcal serogroups in adolescents and adults compared with other meningococcal vaccines [21, 87]. There is good evidence that being a conjugate vaccine it is likely to be more immunogenic in children aged <2 years and to elicit longer-lasting immune protection [88, 89]. The meningococcal C conjugate vaccine is approximately 87–98% effective in preventing meningococcal serotype C infection in infants and young children for a relatively long duration of time [7, 90].

Pneumococcal disease

Indication All travellers aged 2 months to 2 years should be up to date with pneumococcal vaccination following the routine childhood immunisation programme. Immunisation of travellers aged 2–65 years is only recommended for those with chronic medical conditions and at increased risk of severe pneumococcal infection, including travellers with diabetes, splenic dysfunction, immunosuppression and chronic respiratory disease [2].

Vaccine Two types of pneumococcal vaccine are licensed in the UK, both of which are very well tolerated. The pneumococcal polysaccharide vaccine (PPV) contains polysaccharide antigens from 23 different capsular types of pneumococcus, which are responsible for the majority of serious pneumococcal infections in the UK. The pneumococcal conjugate vaccine (PCV) contains polysaccharide antigens from the 13 most prevalent capsular types of streptococcus pneumonia in the US conjugated to a diphtheria CRM197 toxin protein adjuvant, making it more immunogenic, especially in children aged less than 2 years [2]. In 2010, Prevenar-13 was approved in the UK to replace Prevenar-7, which contained only seven streptococcus pneumonia capsular serotype antigens.

Schedule For infants under 1 year of age, the recommended primary course of PCV vaccination includes two doses administered at an interval of 2 months between each dose. The recommended age for vaccination is between 2 and 4 months.

For children from 1 year to under 2 years of age, it is recommended that the primary course of PCV consists of one dose. If the primary course in children under one year is not completed, then a single booster dose of PCV should be given at least 1 month after the last dose to complete the course.

A booster dose of PCV is recommended at between 12 and 13 months of age (i.e. within a month of the first birthday) for children who have received a complete primary course of two PCVs. This vaccine is given at the same time as Hib/MenC and MMR vaccines.

For adults 65 years or over, it is recommended that a single dose of pneumococcal polysaccharide vaccine (PPV) should be administered [2].

Efficacy The 23 serotypes contained within the PPV vaccine are responsible for approximately 96% of serious pneumococcal infections in the UK. More than 80% of adults produce a significant antibody response 3 weeks post PPV vaccination, providing between 50% and 70% protection against pneumococcal bacteraemia, pneumonia and meningitis, but not against other types of infection such as otitis media, chronic bronchitis and pneumonia without bacteraemia [91, 92]. The length of protection provided may vary between the capsular types in the vaccine but typically lasts for up to 5 years. The immune response and protection provided is less effective in travellers aged less than 2 years or with immunosupression, splenic dysfunction or nephritic syndrome [2].

The seven serotypes contained within the PCV vaccine are responsible for approximately 89% of serious invasive pneumococcal infections in the US. PCV vaccine is approximately 97% effective in preventing infection against the seven serotypes, including against pneumococcal pneumonia, meningitis, bacteraemia and otitis media [93]. The vaccine has led to a significant reduction in invasive pneumococcal disease overall and it provides significant herd immunity against these seven serotypes, although there has been a slight increase in invasive pneumococcal disease from other serotypes not included in the vaccine. Trials suggest that the PCV Prevenar-13 vaccine is equally as effective as Prevenar-7 in protecting against invasive pneumococcal disease for the shared serotypes and provides additional protection against the additional six serotypes contained in the vaccine responsible for the majority of the pneumococcal infections not covered by Prevenar-7 [4, 87]. Children who began their immunisation schedule with Prevenar-7 should complete it with Prevenar-13.

Polio

Indication Travellers should be up to date with the routine polio immunisation schedule in the UK; a booster dose is recommended at 10-yearly intervals for continued protection. A booster of polio vaccine should also be considered for those travelling to or from regions where poliomyelitis is endemic (Nigeria, Pakistan and Afghanistan), and to where there are epidemics, see http://www.polioeradication.org/casecount.asp [1, 2]. This is particularly the case for travellers who are going to be working in local communities, including healthcare workers and laboratory personnel who may be at increased risk of exposure to poliomyelitis. Saudi Arabia is one country that requires proof of polio immunisation for travellers arriving from polio-endemic countries [1, 2].

Vaccine Two types of polio vaccine, inactivated polio vaccine (IPV) and live oral polio vaccine (OPV), are licensed and since 2004, only IPV is recommended for administration as part of the routine childhood immunisation programme and as a travel vaccination, with OPV being reserved for administration during outbreaks of poliomyelitis [77].

OPV contains live attenuated polio virus serotypes 1, 2 and 3, which replicate in the gastrointestinal tract inducing local mucosal immunity, which reduces the risk of asymptomatic poliomyelitis infection. WHO thus recommends OPV for everyone living in polio-endemic regions, with an additional dose of OPV being administered 1 to 12 months prior to travel to a polio-free country to reduce the risk of transmission through asymptomatic carriage [1]. OPV is shed in the stool for up to 6 weeks, inducing protection in unvaccinated contacts leading to community through herd immunity as well as individual protection. Care must be taken to avoid contact with immunocompromised people during this period. Very rarely, through back-mutations, the live attenuated OPV may cause paralytic poliomyelitis (1.4–3.4 per million doses) [1].

In the UK, IPV is only available in combination with tetanus, diphtheria, pertussis and/or Hib-containing vaccines and it contains inactivated polio virus serotypes 1, 2 and 3. IPV provides very good individual protection against poliomyelitis without the risk of live oral vaccine-associated paralytic poliomyelitis. Although IPV does not provide the enhanced herd immunity and concomitant community protection afforded by OPV, the risk of importation of wild-type poliovirus is now so low that this benefit is less significant than the potential very rare but severe side effects associated with OPV. Localised pain, swelling, erythema and a mild fever are common side effects with IPV vaccination [2].

Schedule The routine immunisation schedule in the UK for IPV consists of three primary doses administered at monthly intervals followed by booster doses every 10 years for travellers to epidemic or endemic areas of polio. In the UK, recommended 10-yearly booster doses of tetanus (Td/IPV) also provide a booster for polio and diphtheria. Travellers who commenced their schedule with OPV can complete the course with IPV [2].

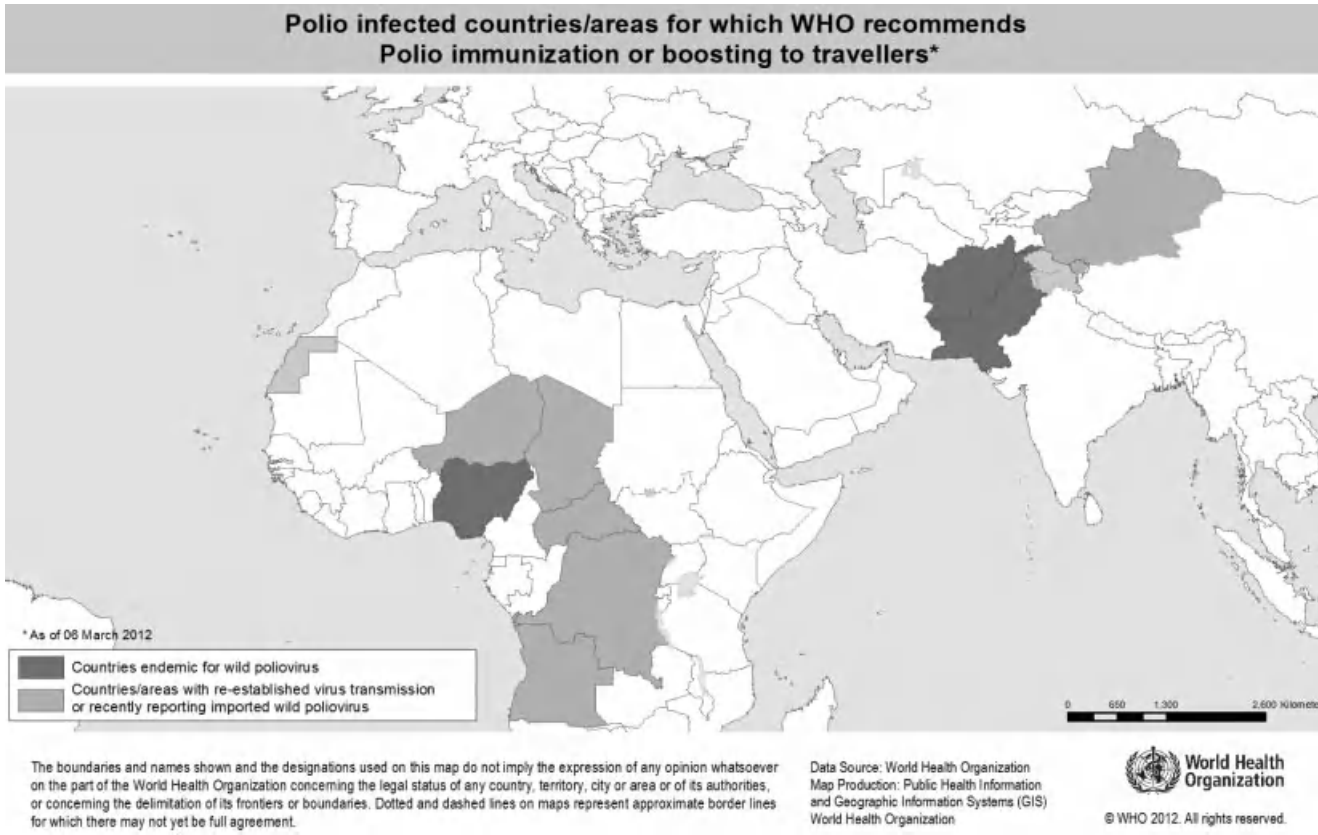

Figure 14.5 Polio-infected countries/ares for which WHO recommends polio immunisation or boosting to travellers.

Efficacy IPV is 95–100% effective in inducing antibodies and providing protection against polio infection for many years. Booster doses every 10 years are then only recommended for travellers living in or travelling to endemic areas [2, 3].

Rabies

Indication More than 50,000 deaths from rabies occur annually worldwide [3]. Classical rabies is enzootic (high risk), especially in wild dogs and bats, in much of Asia, Africa, and Central and South America. Rabies also remains prevalent in much of eastern Europe (*see* Figure 14.6). Most other countries, including most of western and central Europe, are considered low or no risk (rabies-free). A classification of no risk does not include the potential risk arising from bats and so rabies infection may still occur. An updated list of rabies risk by country can be find on the WHO's Rabies Bulletin Europe (www.who-rabies-bulletin.org), Rabnet (www.who.int/rabies/rabnet) or the epidemiology website of the Centers for Disease Control and Prevention (CDC), US (www.cdc.gov/ncidod/dvrd/rabies/epidemiology/epidemiology.htm) [1–3].

In the UK, rabies vaccination is recommended for all travellers aged >1 month travelling to rabies-enzootic regions for durations longer than 1 month, where satisfactory post-exposure medical care is more than 24 hours away, who are likely to engage in outdoor activities, and/or for child travellers. Human rabies immunoglobulin is in scarce supply in many developing countries, and so may be supplies of rabies vaccine. Vaccination is also recommended for travellers working with animals in both high- and low-risk rabies areas, such as veterinary surgeons, zoologists, bat workers and cavers [2].

Vaccine Two inactivated rabies vaccine are licensed in the UK [2]. Common side effects include localised pain and swelling (50%), headache, nausea and abdominal pain (5–40%) [4]. Guillain-Barré Syndrome and other neurological conditions have been reported extremely rarely following rabies vaccination but no causal association has been established.

Schedule The primary immunisation schedule consists of three intramuscular 1.0 ml doses administered on day 0, 7

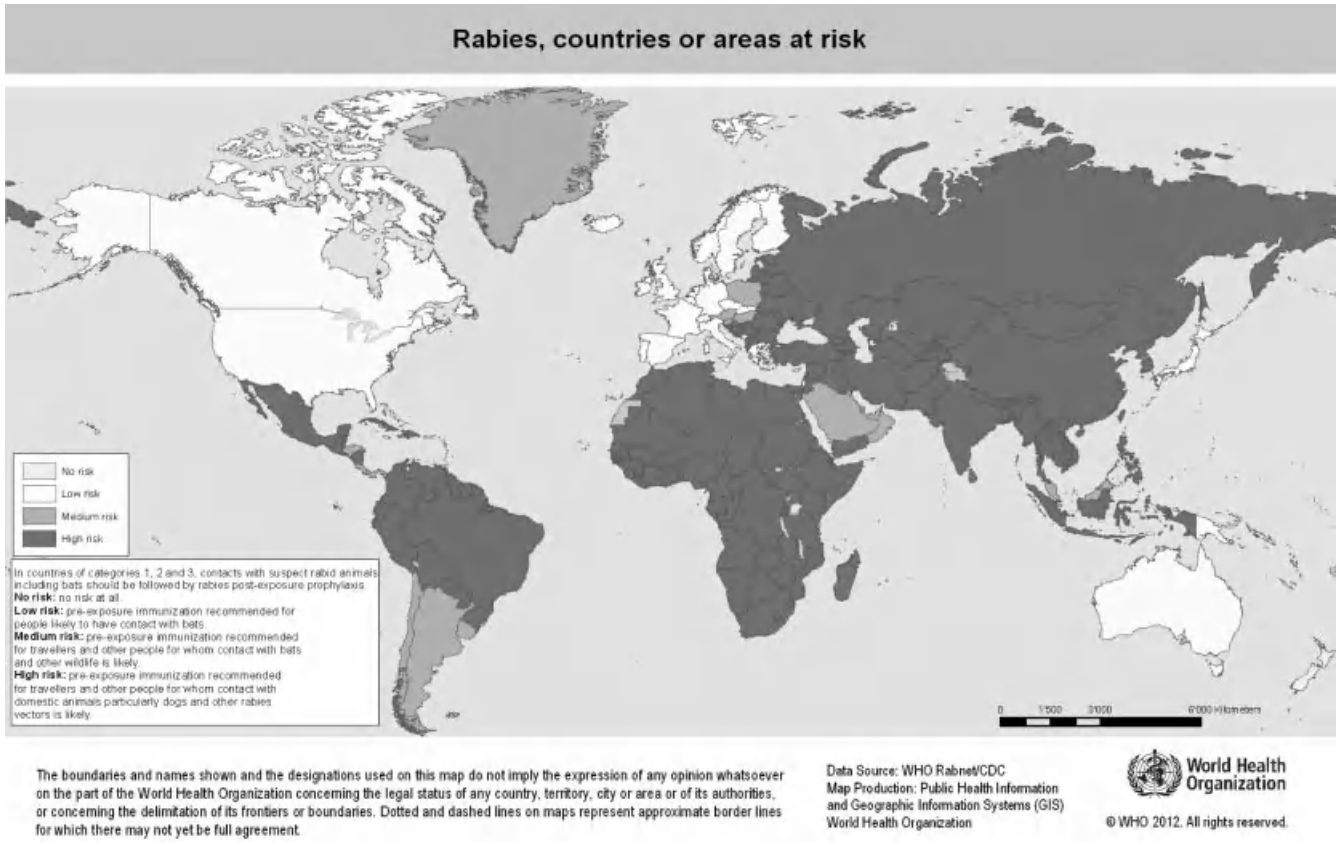

Figure 14.6 Rabies, countries or areas at risk.

and 28, or an accelerated schedule over 21 days with a booster dose at 1 year for those at regular and continuous risk, and then further boosters every 3–5 years. Those travellers who are at intermittent risk or revisiting infected areas are recommended to receive a booster dose administered 2 years following a full primary course [2]. WHO also recommends a more economically efficient schedule for those residing in developing countries consisting of three intradermal 0.1 ml doses administered on days 0, 7 and 28. Chloroquine may inhibit the immune response to intradermal rabies vaccination and so this schedule should be avoided in travellers taking such malaria prophylaxis [1].

Efficacy The overall failure rate for cell culture rabies vaccines is estimated to be <1 case per 80,000 treatments, but this does not circumvent the need for the post-exposure administration of rabies vaccine [94]. A course of pre-exposure rabies vaccination, however, provides a significant level of protection and may modify the post-exposure management such that rabies-specific immunoglobulin may not need to be administered and fewer doses of post-exposure rabies vaccine may be required. Intramuscular vaccination is slightly more immunogenic than administration using the intradermal route. Rabies vaccines containing classical rabies virus provide a varying degree of cross-protection against rabies-related lyssaviruses [95].

Post-exposure prophylaxis Following a potential risk of exposure to infection with rabies, a risk assessment based on the local incidence of rabies, behaviour characteristics of the animal involved and nature of the exposure should be undertaken. Rabies is more common in certain mammals such as dogs, cats, bats, foxes and raccoons than others such as rats, squirrels and cattle. Rabies infection is more likely in unprovoked attacks from animals with frantic or paralysed behaviour. If possible the animal should be tested for rabies or observed for behavioural changes (for 10 days in the case of dogs and cats), although this should not delay the start of post-exposure prophylaxis [7]. A traveller who wakes up in a room with a bat should seek local medical advice regarding an assessment for the risk of rabies, depending on the local bat epidemiology, as a bat bite or scratch may go unnoticed and may not be visible. Bites and proximal wounds such as those on the hands and face where there is a high density of nerve endings are a higher risk for infection than scratches, mucous membrane contact and more distal wounds [4].

Rabies virus travels to the brain via nerves and not in the bloodstream. Prevention of the virus reaching the brain in travellers exposed to a potential source of rabies may therefore be achieved by thorough wound or mucous membrane cleaning, rabies vaccination and/or wound infiltration with human rabies immunoglobulin. Post-exposure prophylaxis should begin immediately within 24 hours of exposure, but if delayed can be commenced any time after exposure since the incubation time of rabies infection maybe days to years. There are no contraindications to post-exposure prophylaxis since the risk of rabies outweighs any potential vaccine adverse effects [2, 3].

Fully vaccinated travellers should receive only two further doses of rabies vaccine on day 0 and day 3 for both low- and high-risk exposures [2]. Unvaccinated and partially vaccinated travellers exposed to a low risk of rabies infection should receive five intramuscular doses of rabies vaccine on days 0, 3, 7, 14 and 28 (Essen regimen). The WHO recommends four doses, with two on day 0 (one in each deltoid muscle), and a single dose on day 7 and 21 (Zagreb regimen). If the risk of exposure is high, they should also receive 20 IU/kg of human rabies immunoglobulin (HRIG) infiltrated into and around the wound on day 0. For small wounds, any remaining HRIG should be administered intramuscularly. For large wounds the HRIG should be diluted with normal saline to ensure that the entire wound is infiltrated. HRIG can be administered up to 7 days after receiving rabies vaccination and provides rapid protection until an adequate immune response has been induced through vaccination [2].

WHO also recommends a more economically efficient schedule for those residing in developing countries consisting of the intradermal administration of 0.1 ml doses of rabies vaccine. Such post exposure intradermal regimens consist of either 8 or 14 doses depending on the type of rabies vaccine used. The 8 dose regimen consists of two doses in each deltoid on days 0, 3, 7 and 28. The 14 dose regimen consists of 8 doses on day 0 (each deltoid, each suprascapular region, each anterolateral thigh, and the left and right lower abdominal quadrants), 4 doses on day 7 (each deltoid and each anterolateral thigh), a single dose on day 30, and a single dose on day 90 [1].

Rabies vaccines prepared in animal brain tissue and consisting of 5 ml/dose are still available in some developing countries and should be avoided for post-exposure prophylaxis. If HRIG is not available in a developing country, equine rabies immunoglobulin may be used [4].

Tetanus, diphtheria and pertussis

Indication All travellers aged >2 months should be up to date with the routine childhood immunisation programme for tetanus, diphtheria and pertussis, and tetanus boosters are routinely recommended every 10 years. Indeed, all travellers should be up to date, especially those travelling to regions with limited medical facilities in case human tetanus immunoglobulin is not available following a tetanus-prone wound [2].

Unimmunised travellers born before 1940 may be considered naturally immune to diphtheria. Adult travellers whose last dose of diphtheria vaccine was more than 10 years ago should have a booster dose if they are travelling to regions where diphtheria is endemic or there is an epidemic. This includes travel to Africa, the Indian subcontinent, Southeast Asia and South America. Healthcare workers, laboratory personnel and other travellers living and working within local communities in such regions are at particularly increased risk of exposure to diphtheria [2]. Pertussis vaccination is not routinely recommended in the UK for children aged >10 years or adults who are travelling, and monovalent pertussis vaccine is not available in the UK. In many other countries, such as Australia, the US and Canada, pertussis vaccination is administered as a booster dose as part of the national vaccination schedule and may be considered for adolescents and adults travelling to developing countries where there is a risk of exposure to infection [1, 4].

Vaccine In the UK, intramuscular tetanus, diphtheria and pertussis vaccines are only available in combination for infants and children as Pediacel (DTaP/IPV/Hib), Repevax (dTaP/IPV), Infanrix-IPV (DTap/IPV), and for adults as Revaxis (Td/IPV) [2]. Two strengths of the diphtheria and pertussis components exist, a stronger more immunogenic dose 'D' (>/30 IU diphtheria toxoid) and 'aP' (five pertussis antigen components) for the primary immunisation of travellers aged 6 weeks to 10 years, and a smaller dose 'd' (2 IU diphtheria toxoid) and 'ap' (three pertussis antigen components) for travellers aged >10 years. The lower-strength diphtheria and pertussis vaccines have less risk of inducing vaccine-associated adverse reactions while remaining sufficiently immunogenic in the older age group (but not in younger travellers) [2]. The choice of combination vaccine will also depend on the need to provide protection against the other component vaccines.

Side effects may include localised pain, swelling and erythema (25%), unilateral limb swelling (3%), vomiting (2%), persistent crying (1:1,000), seizures (1:14,000), high fever (1:16,000) and anaphylaxis (< 1:1,000,000) [4]. A very rare side effect of tetanus-containing vaccines is brachial neuritis post tetanus vaccination (5–10 per million doses) [1].

Schedule The primary immunisation schedule for tetanus consists of three doses administered at 3–monthly intervals followed by a booster dose at 1–3 years and a second booster dose at 5–10 years. Subsequent booster doses should then be given routinely every 10 years. After the age of 10 years,

booster doses are normally given with Revaxis (Td/IPV). Repevax (dTaP/IPV), which contains diphtheria, tetanus, pertussis and polio, is licensed for use in the UK but is not administered routinely as a booster dose for adolescents or adults.

Efficacy The diphtheria, acellular pertussis and tetanus components are approximately 97%, 92% and 100% effective respectively in preventing infection [3, 96–98].

Post-exposure tetanus prophylaxis Travellers are considered fully immunised against tetanus if they have received a primary course of tetanus vaccine with a booster dose within the previous 10 years [1, 2]. For travellers to areas where medical attention may not be accessible and whose last dose of a tetanus-containing vaccine was more than 10 years previously, a booster dose should be given prior to travelling, even if the individual has received five doses of tetanus vaccine previously. This is a precautionary measure in case immunoglobulin is not available to the individual should a tetanus-prone injury occur.

A dose of human tetanus immunoglobulin is only recommended for fully immunised travellers with high-risk, heavily contaminated wounds or with extensive devitalised tissue [2]. Travellers exposed to a tetanus-prone wound who are non-immune (either unvaccinated, incompletely vaccinated or whose boosters are not up to date) should have a dose of tetanus vaccine, complete their primary immunisation course of tetanus vaccination if still incomplete, and receive a dose of human tetanus immunoglobulin. For those travellers who are not protected against tetanus, post-exposure doses of tetanus vaccine do not induce a sufficient immune response within the relatively short incubation time of tetanus infection, but will protect the traveller from future exposure [2]. Booster tetanus vaccine doses and human tetanus immunoglobulin are not recommended for clean wounds, even in non-immune travellers. Particular care should be taken with immunocompromised travellers even if they have been fully immunised, because they might not have mounted a sufficient immune response [2, 3]. Human tetanus immunoglobulin is administered as a single 1 ml (250 IU) intramuscular injection. This dose is doubled to 2 ml (500 IU) for contaminated burns, high-risk wounds and if more than 24 hours has elapsed since the injury. Human tetanus immunoglobulin is also used in the treatment of suspected and confirmed cases of tetanus with a dose of 5,000–10,000 IU by intravenous infusion or multiple divided intramuscular injections [2].

Tick-borne encephalitis

Indication Vaccination against tick-borne encephalitis should be considered for all travellers aged >1 year to endemic regions, especially if they are partaking in high-risk activities such as hiking, camping, farming and forestry. This includes travel to many of the forested regions of central and eastern Europe, Scandinavia, large parts of Russia and Siberia, and northern and eastern China, particularly during the spring and summer months [2].

Vaccine Tick-borne encephalitis vaccine is very well tolerated and it is contraindicated in travellers with known anaphylactic reactions to egg products or other components of the vaccine [2].

Schedule The primary immunisation schedule for tick-borne encephalitis vaccine consists of two doses administered over 1 month or an accelerated course over 2 weeks with booster doses administered at 3- to 5–yearly intervals. In some countries such as Austria it is part of the national immunisation schedule [2].

Efficacy Tick-borne encephalitis vaccine is effective against the European and probably the Far East (but not Siberian) subtype of tick-borne encephalitis, providing up to 98% protection [3].

Tuberculosis

Indication In the UK, vaccination against TB is recommended for unvaccinated tuberculin skin testing-negative travellers from birth to adulthood at increased risk of exposure. This includes healthcare professionals, laboratory personnel and all those travelling for longer than 3 months to regions with a high (≥40 per 100,000) annual incidence of TB. Many countries in Africa, South and Central America, Southeast Asia and the Indian subcontinent have a high annual incidence of TB. Although vaccination against TB is no longer part of the routine childhood immunisation programme in the UK, vaccination of travellers aged <16 years who may be at increased risk of exposure is important since they are at increased risk of severe TB infection. This includes children travelling to or having lived in a country or region with a high incidence of TB for longer than 3 months, or if they have a parent or grandparent who was born in such a country. This policy is in accordance with the WHO recommendations for routine immunisation of children living in countries with a high prevalence of TB and for selective immunisation of high-risk children living in low-risk countries [1, 2, 99].

A tuberculin skin test is recommended before TB vaccination in travellers aged >6 years and in travellers who have been exposed to TB [2].

Vaccine In the UK, the bacillus Calmette-Guérin (BCG) vaccine consists of a live attenuated strain of *Mycobacterium*

bovis. It is administered by intradermal injection into the lateral part of the left upper arm at the level of the insertion of the deltoid muscle [2]. The normal response to BCG vaccination is slight induration at the injection site, which develops into a papule that may ulcerate and be associated with regional lymphadenopathy (<1 cm) before healing over several weeks, leaving a small scar. Rare but severe local side effects are usually due to poor administration technique, wrong dosage or inadvertently vaccinating tuberculin-positive travellers. Injection into the shoulder tip predisposes to large keloid scars, subcutaneous injection predisposes to abscess formation, and covering an oozing injection site with an impervious dressings results in delayed healing and a larger scar. Other rare side effects include regional lymphadenopathy (>1 cm), suppurative lymphadenitis (100–1,000 per million doses), osteitis, osteomyelitis and disseminated BCG infection (0.19–1.56 per million doses), which may need to be treated with rifampicin and isoniazid [1, 2]. Other vaccines may be given at the same time as BCG but not in the same limb for at least 3 months due to the risk of regional lymphadenitis. BCG vaccination is contraindicated in travellers who have previously had TB infection, been vaccinated with BCG, have a positive tuberculin skin test or are immunocompromised, including travellers with HIV [2].

Schedule The primary schedule in newborns, children and adults is a single intradermal dose. Booster doses are not recommended [2].

Efficacy The BCG vaccine is not very immunogenic and is no longer used in many countries where two-step tuberculin skin testing is preferred (see US section). It provides 70–80% protection against severe miliary TB and TB meningitis in infants and young children. It is less effective in protecting against pulmonary TB in adults and the efficacy in travellers aged >35 years is very poorly established [2, 99, 100]. Overall protection from tuberculosis infection is only about 51%. BCG is not usually recommended for travellers aged >45 years because most will have had some natural exposure. However, all tuberculin-negative travellers, including those aged >45 years, can be vaccinated with BCG if the risk of TB exposure is high. Protection begins within 6–8 weeks post-vaccination and probably lasts 10–15 years before it begins to wane. Booster doses are not recommended as there is no evidence of significant additional protection but there is an increased risk of side effects [2, 3, 100, 101].

Tuberculin skin testing Tuberculin skin testing is recommended prior to BCG vaccination for all unvaccinated travellers aged >6 years, all travellers without a characteristic BCG scar who are uncertain whether they have had BCG vaccination, and for all travellers who have been exposed to TB in the past or are at increased risk of previous exposure. It is not recommended post-vaccination as further booster doses of BCG are not recommended. Tuberculin skin testing is also used as a method of screening for evidence of infection in both unvaccinated and vaccinated travellers for latent or active TB post exposure. It may take up to 6 weeks following an exposure for tuberculin sensitivity to develop and so a negative result should be repeated at 6 weeks.

Tuberculin purified protein derivative (PPD) consists of protein antigens from seven strains of *M. tuberculosis*. The Mantoux test involves the intradermal injection of 0.1 ml of PPD into the flexor surface of the left forearm to form a 7 mm bleb. Within 48–72 hours of administration, the area of induration at the injection site is measured. A positive result is due to a type four hypersensitivity reaction due to previous exposure to mycobacteria. A positive result may be due to latent or active tuberculosis or non-tuberculosis mycobacteria infection, or previous BCG vaccination. False-negatives may occur, for example in travellers who are immunosuppressed, including with HIV, or malnourished. Results, particularly for screening for infection, should always be interpreted along with any clinical symptoms, known risk of exposure, and other test results including sputum smears and culture, a chest X-ray, histopathology and a Quantiferon blood test, which is more specific for exposure to *M. tuberculosis* [2, 3].

Typhoid fever

Indication Typhoid fever is present worldwide and affects an estimated 22 million people per annum, resulting in approximately 200,000 deaths [4]. The risk of infection in unvaccinated travellers to India is estimated at 300 per 100,000 per month of stay and the importance of vaccination cannot be overemphasised, with the evidence of increasing antibiotic resistance to *Salmonella typhi* in South Asia [4]. Vaccination is recommended for all travellers aged >2 years travelling to endemic areas of typhoid fever, including the Indian subcontinent, parts of Southeast Asia and the Middle East, Africa, and South and Central America, where hygiene and sanitation are poor [102]. Combined hepatitis A and typhoid vaccines can be used when protection against both hepatitis A and typhoid are required [2].

Vaccine Both live and inactivated typhoid vaccines are licensed; the live oral typhoid vaccine consists of attenuated Ty21a strain of *Salmonella typhi*, and combined polysaccharide typhoid and hepatitis A vaccines are licensed similarly (see Hepatitis A section) [2].

The most common side effects associated with the Ty21a vaccine are gastrointestinal upset and influenza-like symptoms. Antibiotics should be avoided 3 days before and after

vaccination with Ty21a to avoid the theoretical risk of interaction. Vaccination should be postponed in travellers with diarrhoea and vomiting until recovery. Ty21a is contraindicated in travellers who are imunocompromised (including HIV) or pregnant [2]. Side effects with the inactivated typhoid vaccines include fever, headache (20%), localised pain and erythema [4].

Schedule The Ty21a vaccine is licensed for administration to travellers aged >6 years and consists of three oral capsules, the first administered on day 1, the second on day 3 and the third on day 5. Booster doses comprise of the complete course of three capsules administered over 4 days and are recommended annually for travellers travelling from non-endemic areas to endemic regions [1].

The monovalent polysaccharide typhoid vaccine is licensed for administration to travellers aged >2 years and comprises of a single dose only, with booster doses administered every 3 years for continued protection. This vaccine may be considered for travellers aged 1–2 years, although polysaccharide vaccines are poorly immunogenic in travellers aged <2 years and advice regarding strict food and water hygiene is an essential adjunct to vaccination [2].

Efficacy The live oral and inactivated polysaccharide typhoid vaccines provide only 55–78% protection [3, 4, 103–105]. It is therefore essential that travellers are advised about the importance of strict personal, food and water hygiene. Vaccination does not provide protection against *Salmonella paratyphi* [2].

Varicella

Indication Travellers who have had chickenpox or herpes zoster infection should be considered naturally immune and varicella serology should be performed to confirm non-immune status before vaccination. Varicella vaccination is not currently part of the routine childhood immunisation programme in the UK nor routinely recommended for non-immune women of child-bearing age as it is in other countries [2].

Varicella zoster virus is present worldwide and in temperate climates many adults are seropositive from childhood exposure. Varicella zoster virus is more common in tropical countries, but despite this, infection occurs predominantly in adolescents and adults. Many indigenous adults in tropical countries are thus seronegative and at increased risk of severe varicella infection [106]. Therefore varicella vaccination should be considered for all non-immune travellers, especially women of child-bearing age planning to live in close proximity with local indigenous people in tropical countries. Vaccination should also be considered for non-immune travellers and immigrants from tropical to temperate climates as they may be seronegative and at risk of infection from the indigenous population to which they migrate. Consequently, if the same group return to their country of origin for a visit, they may inadvertently transmit varicella infection to those that they visit [1].

Vaccine Two live varicella vaccines are licensed in the UK and their side effects may include a localised or generalised vesicular or papular rash in the first month after vaccination (10% adults, 5% children) [2, 107]. Very rarely, the vaccine virus can establish latent infection and reactivate to cause herpes zoster infection, although this risk is much lower than the risk from wild varicella virus. The vaccine is contraindicated in travellers who are pregnant, immunocompromised or who have had an anaphylactic reaction to any of the vaccines' constituent parts [4].

Schedule The primary immunisation schedule in travellers aged 1–13 years consists of a single dose and for travellers aged >13 years two doses over 1 month. Further booster doses are not recommended [2].

Efficacy Seroconversion rates of 97% have been demonstrated in infants receiving one dose of vaccine, with consistently high levels of antibody present for up to 10 years following completion of the course. In recipients aged >13 years, approximately 78% seroconvert after the first dose, rising to 99% after completion of the course. The vaccine provides up to 90% protection in young children and 75% protection in adolescents and adults against chicken pox [2, 107, 108]. Most of the individuals with breakthrough infections have milder clinical courses.

Post-exposure prophylaxis Immunocompromised and non-immune pregnant travellers should be offered human varicella zoster immunoglobulin within 10 days of a significant exposure to varicella zoster [2]. Varicella vaccine alone may also be administered to non-immune individuals up to 3 days following varicella zoster virus exposure, where it may prevent chickenpox infection, although this use is not routine [108].

Yellow fever

Indication Yellow fever is endemic in certain jungle regions of Africa and South America. It has never occurred in Asia, although in many Asian countries the vector for transmission is present. During the period 1970 to 2010, there have been nine reported cases of yellow fever infection, of which eight were fatal, occurring in unvaccinated North American

and European travellers. Of these, only one reported case of yellow fever infection occurred in a traveller who was vaccinated [3, 4]. Many countries where yellow fever is endemic or where there are mosquito vectors and non-human primate hosts require an International Certificate of Vaccination and Prophylaxis (ICVP) under the WHO International Health Regulations, for entry of travellers arriving from, or who have been in transit through, endemic countries. Some countries require a certificate for all travellers and others do not have any yellow fever requirements. These requirements are to limit the spread of or potential importation and introduction of yellow fever in a country. This list is updated on an annual basis on the WHO website (www.who.int/ith). The vaccine can only be administered in yellow fever-designated centres that are designated to issue such certificates [1].

WHO recommends yellow fever vaccination for individuals travelling to endemic areas in sub-Saharan Africa (*see* Figure 14.7) or Central and South America (*see* Figure 14.8), especially if the risk of contracting yellow fever outweighs the rare but potentially serious adverse effects of the vaccine. Yellow fever occurs both endemically and in epidemics, when the risk of transmission is higher. In West Africa, endemic yellow fever occurs in a jungle cycle, savannah cycle and urban cycle involving mosquitoes and humans [109]. This risk is greatest at the end of the rainy season from July to October [4]. In South America, endemic yellow fever is primarily a jungle cycle involving non-human primates, with humans becoming infected when they enter the jungle. The risk is greatest during the rainy season between January and May [4]. A careful risk assessment should be carried out to determine the risk of yellow fever based on the travel itinerary and the risk of adverse events associated with administration of the vaccine. The vaccine should also be considered in individuals travelling to a country where an International Yellow Fever Vaccination Certificate is a requirement. It is important to note that a traveller may be exposed to yellow fever in a country that does not require yellow fever vaccination [1]. Also there are some regions in Africa and South America where yellow fever virus is present but there is a lack

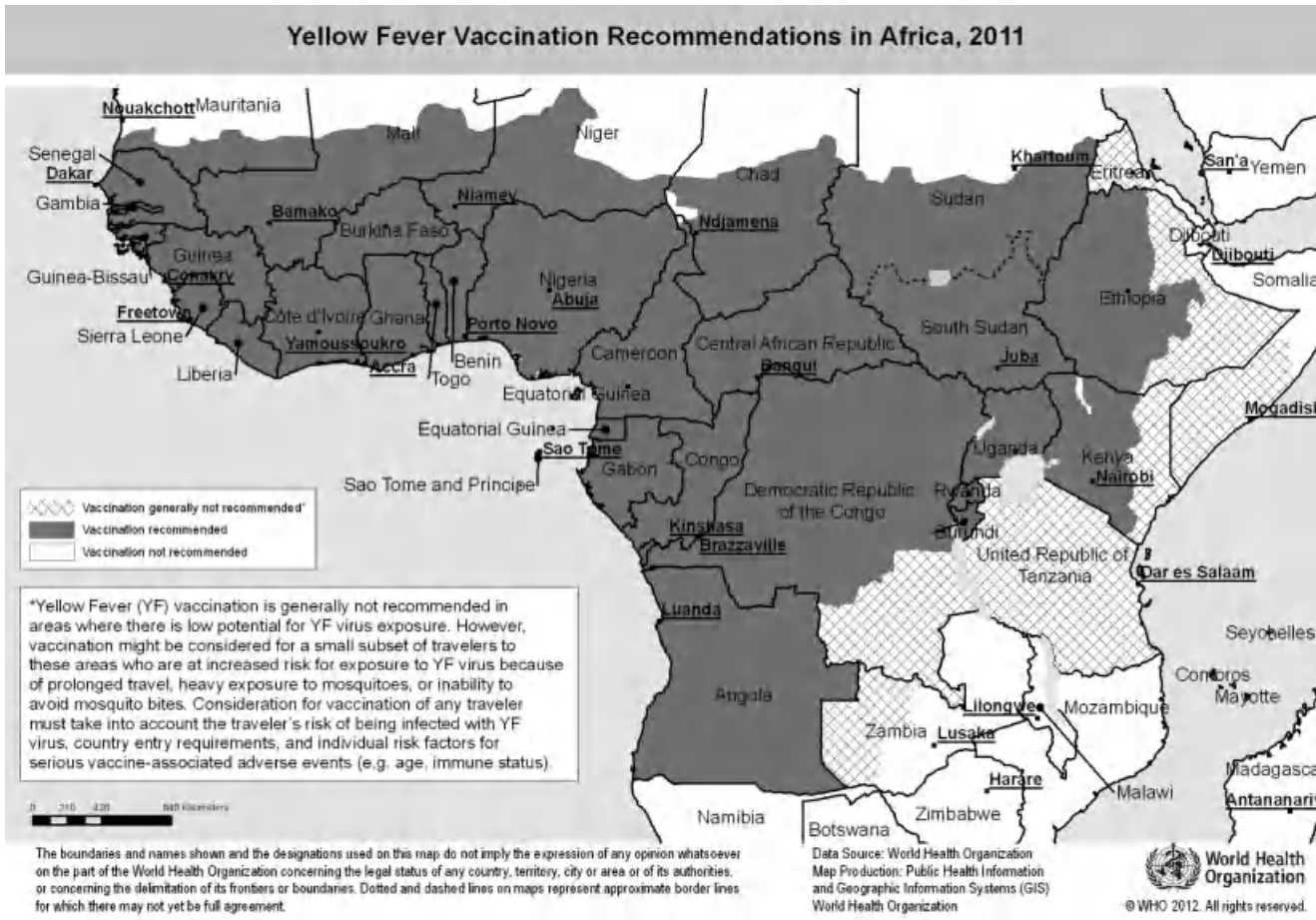

Figure 14.7 Yellow fever vaccination recommendations in Africa, 2011.

Figure 14.8 Yellow fever vaccine recommendations in the Americas, 2011.

of reported human cases either due to poor local surveillance, high immunity in the indigenous people or a low level of transmission [4].

Vaccine Yellow fever vaccine is a live attenuated vaccine administered subcutaneously [2]. Vaccine side effects are normally mild and include localised pain, fever, headache and myalgia (30%). Vaccination is contraindicated in travellers who are immunocompromised, pregnant or have had a previous anaphylactic reaction to egg. However, vaccination maybe considered in travellers who are in the third trimester of pregnancy and in travellers with HIV who have a CD4 count >200 and low viral load if the risk of yellow fever exposure is extremely high. Travellers for whom yellow fever vaccination is contraindicated should avoid travel to endemic regions or adopt a strict mosquito bite prevention strategy, particularly in the daytime. For travellers in whom yellow fever vaccination is contraindicated, a letter of exemption can be issued by the yellow fever vaccine centre for travel to countries where an International Certificate of Vaccination and Prophylaxis (ICVP) against yellow fever is required for entry [1, 2].

Yellow fever vaccine-associated encephalitis is a rare neurological adverse reaction that affects infants in whom the

risk is inversely proportional to age, and is known to occur rarely as part of yellow fever vaccine-associated neurological disease (YEL-AND) [3]. Vaccination is contraindicated in travellers aged <6 months where the risk is 500–4,000 per million doses, and only recommended for travellers aged 6–9 months if the risk of yellow fever exposure is unavoidable [1]. Yellow fever vaccine-associated neurological disease (YEL-AND) is a rare adverse reaction that affects non-immune travellers undergoing primary immunisation. It presents 3–28 days post-vaccination and symptoms/signs include fever, headache, confusion, focal neurological deficits, coma and/or Guillain-Barré Syndrome [110]. This risk increases substantially in travellers aged >60 years from 4 to 17 cases per million doses. The cerebrospinal fluid (CSF) contains yellow fever virus IgM antibody, with a raised cell count and protein. There is usually complete recovery [1, 2, 110, 111]. Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) is another rare adverse reaction that effects non-immune travellers undergoing primary immunisation [112, 113]. It presents 2–7 days post-vaccination with symptoms resembling yellow fever infection, including fever, headache, malaise, hepatitis, hypotension, multi-organ failure and death in more than 60% of cases. The risk also increases substantially in travellers aged >60 years from 3 to 20.5 cases per million doses [2]. Travellers who have a thymus disorder or have had a thymectomy are also at increased risk of YEL-AVD and vaccination is contraindicated in such travellers [114]. Yellow fever virus and viral antigens have been detected in patients with YEL-AVD, although there is no evidence the attenuated virus has reverted to a more virulent form [114].

The risk of yellow fever infection in travellers to endemic areas generally outweighs the small risk of vaccine-associated serious adverse events. However, it is important to vaccinate only those travellers at risk of exposure to yellow fever, especially infants and elderly travellers, based on a comprehensive travel health risk assessment [3, 114].

Schedule The primary immunisation schedule for travellers aged >6 months consists of a single dose with booster doses every 10 years for ongoing exposure [2].

Efficacy Yellow fever vaccination provides 95–100% protection in travellers for at least 10 years and probably for life [2, 3, 115–117]. It takes approximately 10 days to mount a sufficient immune response to the vaccine and consequently, the International Yellow Fever Vaccination Certificate becomes valid 10 days post-vaccination and lasts for 10 years. The vaccine should thus be administered at least 10 days prior to departure. For subsequent re-immunisations the certificate is valid immediately if they occur within the 10-year period.

United States and Canadian travel immunisation guidelines

The travel immunisation guidelines and recommendations in the US and Canada share many similarities with each other, and with the national guidelines of the UK and the international guidelines of the WHO. This section reviews these guidelines with specific reference to the main differences.

The US routine vaccination schedule can be found at http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html. Table 14.3 summarises the routine and travel specific vaccines as recommended at the time of writing in the US. For specific information for various populations see the detailed recommendations from the Centers for Disease Control and Prevention (CDC) publishes more detailed national immunisation guidelines in the Health Information for International Travel (the Yellow Book) http://wwwnc.cdc.gov/travel/page/yellowbook-2012-home.htm. CDC recommends that all travellers be up to date on routine recommended vaccines. Detailed Canadian immunisation guidelines are published by the Public Health Agency of Canada in the Canadian Immunization Guide http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-eng.php 2006.

Principle differences

Cholera

Cholera vaccine is not licensed in the US.

In Canada, the inactivated Dukoral cholera vaccine is licensed for travellers to regions of high cholera risk. It also provides up to 50% protection for 3 months against enterotoxigenic *Escherichia coli* and may be considered as part of a preventive strategy against travellers' diarrhoea, for which overall it provides up to 25% protection. This may be particularly beneficial in travellers with chronic medical conditions and immunosuppression at increased risk of severe travellers' diarrhoea, travellers who suffer from recurrent travellers' diarrhoea, and in short-term travellers for whom it is important to avoid diarrhoea, including sportsmen, businessmen and politicians. The schedule for protection against travellers' diarrhoea is different to that for cholera and consists of two doses 1 to 6 weeks apart with boosters every 3 months [7, 32, 34, 35].

A live oral single-dose cholera vaccine (Orochol or Mutacol) was previously available in Canada, Australia and some European countries. It is not recommended for those who travel routinely but is reserved for very high-risk exposure, such as for healthcare professionals working in refugee camps with a cholera outbreak. It provides over 90% protection within 8 days of administration and for up to 6 months; it should not be administered to travellers prescribed

Table 14.3 Travel vaccine summary

Vaccine	Brand Name	Dose	Route	Schedule	Booster	Age
Hepatitis A (adults)	Havrix	1.0 mL (1,440 ELISA units)	IM	0 and 6–12 months	None	≥19 years
	Vaqta	1.0 mL (50 units)	IM	0 and 6–18 months	None	≥19 years
Hepatitis A (pediatric)	Havrix	0.5 mL (720 ELISA units)	IM	0 and 6–12 months	None	1–18 years
	Vaqta	0.5 mL (25 units)	IM	0 and 6–18 months	None	1–18 years
Combined hepatitis A and hepatitis B	Twinrix	1.0 mL (20 μg of hepatitis B antigen and 720 ELISA units of hepatitis A antigen)	IM	0, 1 month, and 6 months; accelerated schedule: days 0, 7, and 21–30, with a fourth dose at 12 months	None	≥18 years
Hepatitis B (adult)	Engerix-B	1.0 mL (20 μg)	IM	0, 1 month, and 6 months; can be given on an accelerated schedule of 0, 1 month, 2 months, and 12 months	None	≥20 years
	Recombivax HB	1.0 mL (10 μg)	IM	0, 1 month, and 6 months	None	≥20 years
Hepatitis B (pediatric)	Engerix-B	0.5 mL (10 μg)	IM	0, 1 month, and 6 months; can be given on an accelerated schedule of 0, 1 month, 2 months, and 12 months. If using an accelerated schedule, give 0.5 mL (10 μg) for ages birth through 10 years and 1.0 mL (20 μg) for ages 11–19 years	None	≤19 years
	Recombivax HB (primary)	0.5 mL (5 μg)	IM	0, 1 month, and 6 months	None	≤19 years
	Recombivax HB (adolescent accelerated)	1.0 mL (10 μg)	IM	0, 4–6 months	None	For ages 11–15 years

Japanese encephalitis	Ixiaro	0.5 mL	IM	0 and 28 days	≥1 year after primary series[1]	≥17 years
Meningococcal conjugate (MenACWY)	Menactra ($MenACWY_D$)	0.5 mL 0.5 mL	IM IM	2-dose primary series separated by 3 months 1 dose	See Chapter 3, Meningococcal Disease See Chapter 3, Meningococcal Disease	9–23 months 2–55 years
	Menveo ($MenACWY_{CRM}$)	0.5 mL	IM	1 dose	See Chapter 3, Meningococcal Disease	2–55 years
Meningococcal polysaccharide (MPSV4)	Menomune	0.5 mL	SC	1 dose	See Chapter 3, Meningococcal Disease	≥2 years
Inactivated polio (adult)	Ipol	0.5 mL	SC or IM	1 dose at ≥18 years, if patient has already had an acceptable polio vaccine series	None	≥18 years
Rabies	Imovax	1.0 mL	IM	Preexposure series: days 0, 7, and 21 or 28	See Chapter 3, Rabies	No age restrictions
	RabAvert	1.0 mL	IM	Preexposure series: days 0, 7, and 21 or 28	See Chapter 3, Rabies	No age restrictions
Typhoid capsular polysaccharide	Typhim Vi	0.5 mL	IM	1 dose	Every 2 years	≥2 years
Typhoid oral, live, attenuated	Vivotif	1 pill	Oral	1 pill every other day for 4 doses	Every 5 years	≥6 years
Yellow fever	YF-Vax	0.5 mL	SC	1 dose	Every 10 years	≥9 months, same dose for children and adults[1]

Abbreviations: ELISA, enzyme-linked immunosorbent assay; IM, intramuscular; SC, subcutaneous.

[1]Special considerations apply in deciding whether to administer yellow fever vaccine. Yellow fever vaccine is never given to infants <6 months and is given with precaution and only under special circumstances for ages 6–8 months. There is also a precaution for its use in patients aged ≥60 years

Table 14.4 Australian travel immunisation schedule

Vaccine	Routine recommended immunisation schedule (age)	Vaccine brand (s)	Route	Age (minimum age, catch-up schedules)	Dose	Primary schedule (recommended schedule expressed as time after 1st dose unless otherwise stated, accelerated schedule, and minimum intervals when different to recommended)	Booster (time after completion of primary schedule unless otherwise stated)
Routine vaccinations							
Hepatitis B (monovalent)	Routine (birth–<18y) 4 doses (birth, 2m, 4m, 6m)	Engerix B	IM	0–<20y	0.5ml (10μg)	3 doses (0, 1m, 6m) OR 4 doses (0, 1m, 2m, 12m (booster))	None
				≥20y	1.0ml (20μg)	3 doses (0, 1m, 6m) OR 4 doses (0, 1m, 2m, 12m (booster)) OR 4-dose accelerated schedule (0, 7d, 21d, 12m (booster))	
				11–<16y	1.0ml (20μg)	2 doses (0, 6m)	
		HBvaxII Paediatric		0–<20y	0.5ml (5μg)	3 doses (0, 1m, 6m)	
		HBvaxII		≥20y	1.0ml (10μg)	3 doses (0, 1m, 6m)	
		HBvaxII Dialysis		≥20y	1.0ml (40μg)	3 doses (0, 1m, 6m)	
Hepatitis B & Hib (combined)	Routine (2m–5y)	Comvax	IM	6w–<6y	0.5ml (10μg HepB)	3 doses (0, 4w, 12w (with 3rd dose after 12m age))	None

Hepatitis B & diphtheria, tetanus, pertusis, IPV and Hib (combined)	Routine (2 m–<5 y)	Infanrix Hexa (DTaP+HepB+ IPV+Hib)	IM	6 w–<7 y	0.5 ml (10 μg Hep B)	3 doses (0, 4 w, 12 w (with 3rd dose after 12 m age))	None
Hepatitis B & diphtheria, tetanus, pertusis, and IPV (combined)	Routine (2 m–<8 y)	Infanrix Penta (DTaP+HepB+IPV)	IM	6 w–<8 y	0.5 ml (10 μg Hep B)	3 doses (0, 4 w, 12 w (with 3rd dose after 12 m age))	None
Hib	Routine (2 m–<5 y) 3 doses (2 m, 4 m, 6 m) Booster at 12 m	Monovalent (Hiberix; PedvaxHIB) Combined (Infanrix Hexa; Comvax)	IM	6 w–<12 m	0.5 ml	3 doses (0, 4 w, 8 w – with 3 doses before 12 m) Only 2 doses with Comvax or PedvaxHIB as more immunogenic	Single booster dose after 12 m age (minimum 8 w after 3rd dose)
				12–<15 m		2 doses (0, 8 w)	None
				15 m–<5 y		1 dose (0)	None
HPV	Routine (12–<26 y) 3 doses (12–13 y at time 0, 2 m, 6 m)	Gardasil Cervarix	IM	9–<26 y 10–<26 y	0.5 ml	3 doses (0, 2 m, 6 m)	None
Influenza	Routine (≥65 y) Annual boosters (≥65 y)	New brands every 6 months depending on circulating strains of influenza	IM	6 m–<3 y 3–<9 y ≥9 y	0.25 ml 0.5 ml 0.5 ml	2 doses (0, 4 w) 1 dose (0)	Annual
Measles, mumps and rubella (MMR)	Routine (≥12 m) 2 doses (12 m, 4 y)	Priorix	IM	9–<12 m ≥12 m	0.5 ml	3 doses (0, after 12 m age, 1 m after 2nd dose) 2 doses (0, 1 m)	None

(*Continued*)

Table 14.4 (*Continued*)

Vaccine	Routine recommended immunisation schedule (age)	Vaccine brand (s)	Route	Age (minimum age, catch-up schedules)	Dose	Primary schedule (recommended schedule expressed as time after 1st dose unless otherwise stated, accelerated schedule, and minimum intervals when different to recommended)	Booster (time after completion of primary schedule unless otherwise stated)
Meningococcal	Routine (12 m) 1 dose of MenC (12 m)	Meningococcal monovalent conjugate:	IM	6 w–<12 m	0.5 ml	3 doses (0, 2 m, 6 m (with two doses <12 m age and 1 dose after 12 m age)	None
		Meningitec					
		Menjugate					
		NeisVac-C		≥12 m		1 dose (0)	
		Meningococcal quadrivalent (A, C, W135, Y) polysaccharide:	SC	≥2 y		1 dose (0)	Every 3–5 y for polysaccharide vaccines
		Mencevax ACWY					Need for booster of Menveo currently not known
		Menomune					
		Meningococcal quadrivalent (A, C, W135, Y) conjugate:					
		Menveo		≥11 y			
		Menactra		2 y–55 y			

Pneumococcal	Routine (PCV 2 m–<2 y; PPV >/65 y) 3 doses of PCV (2 m, 4 m, 6 m) 2 doses of PPV (65 y, 70 y)	PCV: Prevenar 13 PPV: Pneumovax 23	IM	6 w–<12 m 12 m–<18 m 18 m–<2 y ≥65 y	0.5 ml	3 doses (0, 4 w, 8 w – with 3 doses before 12 m age) 2 doses (0, 8 w) 1 dose (0) 1 dose (0)	None None None Single booster at 5 y
Polio (IPV)	Routine (≥2 m) 3 doses (2 m, 4 m, 6 m) Booster at 4 y	Monovalent IPOL Combination: Infanrix-Hexa (DTap+HB+IPV+Hib); Infanrix-IPV (DTap+IPV); Infanrix Penta (DTap+HepB+IPV); Boostrix-IPV (Tdap+IPV); Adacel Polio (TdaP+IPV)	IM	≥6 w	0.5 ml	3 doses (0, 4 w, 6–12 m) OR 3-dose accelerated schedule (0, 4 w, 8 w) (4 doses if 3rd dose given before 4 y age – 0, 4 w, 8 w, 12 w)	Booster every 10 y
Rotavirus	Routine (2 m–<32 w) 3 doses with Rotateq or 2 doses with Rotarix (2 m, 4 m, +/– 6 m)	Rotateq Rotarix	PO	6 w–<32 w 6 w–<24 w	2.0 ml 1.0 ml	3 doses (0 (max age <15 w), 4 w, 8 w (max age <32 w)) 2 doses (0 (max age <15 w), 4 w (max age <24 w))	None

(*Continued*)

Table 14.4 (*Continued*)

Vaccine	Routine recommended immunisation schedule (age)	Vaccine brand (s)	Route	Age (minimum age, catch-up schedules)	Dose	Primary schedule (recommended schedule expressed as time after 1st dose unless otherwise stated, accelerated schedule, and minimum intervals when different to recommended)	Booster (time after completion of primary schedule unless otherwise stated)
Tetanus, diphtheria and pertussis	Routine (≥2 m) 3 doses (2 m, 4 m, 6 m) Booster at 4 y and 12–17 y Single booster ≥50 y	Infanrix-Hexa (DTap+HepB+IPV+Hib); Infanrix-IPV (DTap+IPV); Infanrix Penta (DTap+HepB+IPV)	IM	6 w–<8 y	0.5 ml	3 doses (0, 4 w, 8 w)	Booster 6 m after primary schedule Second booster 6 m after 1st booster if 1st booster was before 4 y age Or Second booster 10 y after 1st booster if 1st booster was after 4 y age Single booster after 50 y age (minimum 10 y after previous booster and one booster dose should be with Tdap)
		Tdap: BOOSTRIX (Tdap); Boostrix-IPV (Tdap+IPV); ADACEL (TdaP)[7]; Adacel Polio (TdaP+IPV); ADT Booster (Td)		≥8 y		3 doses (0, 1 m, 2 m)	2 booster doses at 10 y & 20 y Single booster after 50 y age (minimum 10 y after previous booster) (one of booster doses to be with Tdap; all other boosters with Td)

Varicella	Routine (≥18 m) 1 dose (18 m)	Varilrix Varivax	SC	1–<14 y ≥14 y	0.5 m 0.5 ml			1 dose OR 2 doses (0, 4 w) 2 doses (0, 4 w)	None
Varicella zoster	Routine (≥60 y) 1 dose (60 y)	Zostavax	SC	≥60 y	0.65 ml			1 dose (0)	Under evaluation
Travel vaccinations:									
Cholera	Not routine	Dukoral	PO	2–<6 y ≥6 y	75 ml solution 150 ml solution			3 doses (0, 1–6 w, 1–6 w after 2nd dose) 2 doses (0, 1–6 w)	Every 6 m Every 2 y
Hepatitis A (monovalent)	Not routine	Havrix Monodose Havrix Junior Monodose Avaxim Vaqta Vaqta Paediatric	IM IM IM IM IM	≥16 y 2–<16 y ≥2 y ≥18 y 1–<18 y	1.0 ml (1440 ELISA units) 0.5 ml (720 ELISA units) 0.5 ml (160 antigen units) 1.0 ml (50 antigen units) 0.5 ml (25 antigen units)			1 dose (0)	Booster at 6–12 m
Hepatitis A & B (combined)	Not routine	Twinrix Adult	IM	≥16 y	Dose 1.0 ml	HAV 720 ELISA units	HBV 20 µg	3 doses (0, 1 m, 6 m) OR 4-dose accelerated schedule (0, 7 d, 21 d, 12 m (booster))	None
		Twinrix Junior		1–<16 y	Dose 0.5 ml	HAV 360 ELISA units	HBV 10 µg	3 doses (0, 1 m, 6 m)	
		Twinrix		1–15 y	Dose 1.0 ml	HAV 720 ELISA units	HBV 20 µg	2 doses (0, 6–12 m)	
Hepatitis A & typhoid (combined)	Not routine	ViVAXIM	IM	≥16 y	Dose 1.0 ml	HAV 160 antigen units	Vi P Ty 25 µg	1 dose (0)	Single monovalent Hepatitis A booster at 6–12 m Monovalent typhoid booster every 3 y

(*Continued*)

Table 14.4 (*Continued*)

Vaccine	Routine recommended immunisation schedule (age)	Vaccine brand (s)	Route	Age (minimum age, catch-up schedules)	Dose	Primary schedule (recommended schedule expressed as time after 1st dose unless otherwise stated, accelerated schedule, and minimum intervals when different to recommended)	Booster (time after completion of primary schedule unless otherwise stated)
Influenza A(H1N1)v	Not routine	Panvax	IM	6 m–<3 y 3–<10 y ≥10 y	0.25 ml 0.5 ml 0.5 ml	2 doses (0, 4 w) 1 dose (0)	None
Japanese encephalitis	Not routine	Jespect (IXIARO)	IM	≥18 y	0.5 ml	2 doses (0, 28 d)	Booster doses for Jespect under evaluation
Q fever	Not routine	Q-VAX	IM	≥15 y	0.5 ml	1 dose (0)	None
Rabies	Not routine	Mérieux Rabipur	IM	From birth	1.0 ml	3 doses (0, 7 d, 28 d)	Booster every 2 y if continued high risk
Tuberculosis	Not routine	BCG	ID	≤12 m >12 m	0.05 ml 0.1 ml	1 dose (0)	None
Typhoid	Not routine	Vi polysaccharide: Typhim Vi Typherix Ty21a: Vivotif	IM PO	≥2 y ≥6 y	0.5 ml 1 capsule	1 dose (0) 3–4 doses (0, 2 d, 4 d +/– 6 d)	Every 3 y Boosters of 3 doses every 3 y if 3 doses given initially Boosters of 4 doses every 5 y if 4 doses given initially
Yellow fever	Not routine	Stamaril	SC	≥9 m	0.5 ml	1 dose (0)	Every 10 y

concomitant antimicrobials or chloroquine antimalarial prophylaxis [7, 111].

Hepatitis A

Hepatitis A is part of the routine childhood immunisation programme in the US for all children aged 1–2 years and is recommended for all travellers aged >1 year to regions of high hepatitis A prevalence. However, many travel health experts feel that all travellers should be protected against hepatitis A. Travellers to regions with high hepatitis A prevalence who are aged <1 year, immunocompromised or have chronic medical conditions and are departing within 2 weeks may be offered passive immunisation with human normal immunoglobulin (HNIG), which provides immediate protection for up to 3 months with a dose of 0.02 ml/kg and up to 5 months with 0.06 ml/kg. With the exception of travellers aged <1 year, such travellers should also be vaccinated against hepatitis A at the same time. Hepatitis A vaccine is not available in combination with typhoid vaccine in the US [4].

Hepatitis A is not part of the Canadian routine immunisation schedule but is available for travellers to regions with high hepatitis A prevalence [7].

Hepatitis B

Hepatitis B is part of the routine immunisation schedule in the US. It is available as monovalent hepatitis B vaccine or in combination with hepatitis A, Hib or with tetanus, diphtheria, pertussis and IPV. Combined Hepatitis A and B vaccines are only recommended for travellers aged ≥18 years. An accelerated schedule of three doses of monovalent hepatitis B or combined hepatitis A and B vaccines over 3 weeks with a booster at 12 months may be administered to adult travellers. Other booster doses are not routinely recommended except for travellers with certain underlying medical conditions such as renal failure requiring dialysis [4].

Hepatitis B is also part of the Canadian routine immunisation schedule and the combined hepatitis A and B vaccine Twinrix Junior is available for travellers aged 1–18 years. As in the UK, Twinrix may be given according to the normal three-dose schedule or to travellers aged 11–15 years as a two-dose schedule over 6–12 months [7].

HPV

Two HPV vaccines, a quadrivalent HPV vaccine (HPV4) and a bivalent HPV vaccine (HPV2), are licensed and recommended for use in adolescents and young adults in the US. HPV4 is approved by the Food and Drug Administration (FDA) for girls/women and boys/men aged 9–26 years, and the Advisory Committee on Immunization Practices (ACIP) as of 2011 has recommended HPV4 for routine use among boys and men aged 9–26 years. HPV2 is FDA approved for girls/women aged 10–25 years. HPV2 is not FDA approved for boys or men [4].

Influenza and pandemic influenza

In the US, annual vaccination of all people aged ≥6 months is recommended by CDC and the ACIP. Vaccination of pregnant women and household contacts of children aged <6 months can also reduce the risk of influenza in these children who are too young to receive vaccination. Three types of influenza vaccine are available for use, including a trivalent inactivated vaccine (TIV), administered intramuscularly, and a trivalent live, attenuated vaccine (LAIV), administered by nasal spray. LAIV is approved for use only in healthy people aged 2–49 years who are not pregnant. The third type is that which contains greater antigen, which may be given to older patients.

The most frequent side effects of vaccination with TIV are soreness and redness at the vaccination site that last up to 2 days. Fever, malaise and other systemic symptoms occur less commonly. A high-dose TIV is an option for people aged ≥65 years. The most frequent side effects of LAIV are runny nose or nasal congestion, headache and sore throat. It also may result in an increase in asthma or reactive airway disease in children <5 years of age. It should not be administered to children between 2 and 4 years who have a history of wheezing in the past year or who have a diagnosis of asthma. Both the intramuscular and intranasal vaccines reflect the most prevalent circulating influenza viruses in the northern hemisphere [4].

In Canada, influenza vaccination is routine for children aged 6 months to 2 years and adults aged >65 years [7].

Japanese encephalitis

In the US, IXIARO is the only Japanese encephalitis vaccine and is licensed for travellers aged >17 years. The inactivated mouse-brain JE-VAX is no longer available [4].

The Japanese encephalitis vaccine currently available for use in Canada is JE-VAX. At the time of writing, IXIARO was still awaiting approval for use in Canada [7].

Meningococcal meningitis

Menactra and Menveo, conjugated quadrivalent meningococcal vaccines that have different protein conjugates, are licensed and recommended for travellers aged <55 years. Menactra is the only meningococcal vaccine licensed in the US for children aged 9 months to 2 years. Menomune, a polysaccharide quadrivalent meningococcal vaccine, is licenced and recommended for travellers >2 years. Menactra and Menveo are the preferred vaccines for travellers aged <55

years, while Menomune should be used for travellers aged >55 years [4]. Travellers with splenic dysfunction or other immunosuppressive conditions may need booster doses or enhanced regimens [118, 119].

The routine Canadian immunisation schedule is more similar to that in the UK, with conjugate meningococcal C vaccine (Meningitec, Menjugate or NeisVac-C) recommended for children aged 3 months to 5 years. There are two polysaccharide meningococcal vaccines available, a bivalent meningococcal A and C vaccine called Menomune A/C, and a quadrivalent A, C, W135, Y vaccine called Menomune A/C/Y/W-135, which is the vaccine of choice for international travellers from Canada [7].

Measles, mumps and rubella

Travellers born before 1957 in the US maybe considered naturally immune to measles and mumps. In the US, the recommendation is that those >12 months receive two measles containing vaccine (MCV) doses separated by >28 days. (Infants aged 6–11 months should have at least one MCV does and those vaccinated prior to age 12 months should be revaccinated on or after the first birthday with two doses of MCV. (see http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/measles-rubeola.htm). The UK guidelines are similar in that the primary immunisation schedule for travellers aged <50 years consist of two doses of MMR administered 4 weeks apart or after 12 months of age. Particular emphasis in both the US and UK is placed on ensuring all women of child-bearing age are vaccinated [4]. MMR is also available in combination with varicella vaccine (MMRV) as ProQuad for travellers aged 1–12 years and is administered as two doses with a minimum interval of 3 months [4, 120].

In Canada, individuals born before 1970 may be considered naturally immune to measles. It is recommended that all unvaccinated children aged >1 year should receive two doses of MMR vaccine administered 4 weeks apart and all adults should receive a single dose of MMR [7].

Pneumococcal disease

In 2010, Prevenar-13 was approved in the US to replace Prevenar-7 for the routine immunisation of children aged 6 weeks to 5 years. Prevenar-13 consists of 13 streptococcus pneumonia serotype antigens conjugated to a diphtheria CRM_{197} toxin protein adjuvant. Trials suggest that it is equally as effective as Prevenar-7 in protecting against invasive pneumococcal disease for the shared serotypes and provides additional protection against the additional six serotypes contained in the vaccine responsible for the majority of the pneumococcal infections not covered by Prevenar-7 [4, 87]. Children who began their immunisation schedule with Prevenar-7 are recommended to complete the course with Prevenar-13. Although there are no specific recommendations for this vaccine for travellers, the 23-valent pneumococcal polysaccharide vaccine is recommended for all adults aged ≥65 years of age and for those 2–64 years with underlying medical conditions. Providers should take the opportunity to immunise such individuals prior to travel if they have not already received vaccine.

Rabies

Two rabies vaccines are licensed in the US for administration to travellers from birth if indicated. Booster doses are recommended only for travellers at high risk of exposure, such as veterinarians working in rabies-enzootic areas either every 2 years or based on measured antibody levels every 6 months [4]. New guidelines from the Advisory Committee on Immunization Practices in March 2010 regarding post-exposure rabies prophylaxis recommend the administration of four doses of rabies vaccine (rather than five) on day 0, 3, 7 and 14 and infiltration of HRIG in and around the wound.

Rotavirus

In the US, there are two oral live rotavirus vaccines that are part of the routine childhood immunisation programme from 6 weeks to 8 months of age (8 months being the maximum age for the final dose in the series). Rotarix consists of a single attenuated rotavirus strain, whereas RotaTeq consists of five different attenuated rotavirus strains. The vaccines replicate in the intestinal mucosa and are 85–98% effective in preventing severe rotavirus gastroenteritis. Side effects may include mild gastroenteritis and vaccination should be postponed during gastroenteritis illness, with some studies suggesting a very slight increased risk of intussusception within 1 week following administration of the first dose of vaccine [4]. Rotavirus vaccination, though a universally recommended vaccine in the US, may also help protect young travellers against acute gastroenteritis and severe dehydration in remote locations where oral or intravenous rehydration treatment is not immediately available [4].

Rotavirus is not part of the Canadian routine immunisation schedule.

Tetanus, diphtheria and pertussis

In the US, tetanus is available in a variety of combinations with diphtheria, pertussis, Hib, IPV and hepatitis B vaccines (Table 14.3). The increased antigen-containing doses of diphtheria 'D' and pertussis 'P' are recommended for travellers aged <7 years. The primary immunisation schedule recommended for tetanus vaccination for travellers aged >7 years consists of three doses administered on day 0, 4 weeks and 6 months, although the minimum interval between the second and third dose is 4 weeks. Two of these administered

doses are recommended to include Td and one with TdaP. There are, however, currently no licensed vaccines containing pertussis for those aged between 7 and 10 years. Booster doses are then recommended every 10 years with Td, with at least one of these booster doses being with TdaP. The minimum recommended interval between booster doses is 5 years, although this maybe shorter if the purpose of the vaccine dose is to provide pertussis protection. Unvaccinated pregnant women should also be vaccinated according to this three-dose schedule with two of the doses during the pregnancy and the third dose 6 months later. Pregnant women who have not received a booster dose with Td or TdaP for more than 10 years should have a booster dose during pregnancy. Pregnant women should have received at least one previous booster dose with TdaP since age >11 years or they should receive a dose of TdaP during pregnancy, or in the postpartum period if they are up to date with their Td boosters [4]. Travellers are considered fully immune if they have had three doses of tetanus with the last dose within 10 years [4]. All children and adults who are travelling are recommneded currently to be vaccinated against pertussis due to increasing numbers of cases of pertussis occurring in adults recently [4].

In Canada, the primary schedule for travellers aged 7–18 years consists of three doses of Tdap. The primary schedule for adult travellers consists of two doses of Td and one dose of Tdap [7].

Tuberculosis

In the US, vaccination with BCG is not recommended as part of the routine childhood immunisation programme or for travellers. Instead, a two-step PPD testing regimen is used whereby long-term travellers have a Mantoux test before departing and then again on their return, 6 weeks after the last possible exposure to TB. If either of the two tests is positive the traveller is referred for further investigations and treatment of latent or active TB. This policy has also been adopted by many other countries around the world, including many European countries. Such a policy has several advantages, especially for adult travellers in whom BCG vaccination is less effective in preventing pulmonary TB. The policy removes the potential for false-positive Mantoux results due to BCG vaccination. The greatest risk of conversion from latent to active TB is within the first 2 years of infection. The two-step PPD policy enables close surveillance for the time when travellers become infected with TB and their early treatment thus reducing their risk of developing active disease [4]. In 2001, the FDA approved the quantiFERON-TB test, which is also helpful for diagnosis of latent TB in some patients.

In Canada, BCG vaccine is available, although immunisation is also not routinely recommended for the same reasons as in the US. Travellers to regions with a high incidence of tuberculosis may consider the two-step PPD testing approach as used in the US or may opt for BCG immunisation if regular annual testing is not possible or they are against insonizid treatment should their PPD become positive. Vaccination should also be considered in travellers working as healthcare professionals, and in individuals living in parts of Canada or abroad with a high incidence of tuberculosis [7].

Typhoid

The live oral Ty21a typhoid vaccine (Vivotif) is administered as four doses on days 0, 2, 4 and 6, with a recommendation for repeating the same regimen every 5 years (7 years in Canada) for ongoing exposure. An alternative is the single dose of the inactivated typhoid vaccine (Typhim Vi) for which a repeat dose is recommended every 2 years [7].

Varicella

Persons born before 1980 in the US may be considered naturally immune to varicella. Varicella vaccine is part of the routine childhood immunisation schedule and is available as a monovalent vaccine or in combination with measles, mumps and rubella (MMRV). Vaccination is recommended for all non-immune persons aged >1 year, including non-pregnant women of childbearing age and healthcare workers. The vaccine is administered as two doses for those aged 1–12 years with a minimum recommended interval of 12 weeks between the two doses, although an absolute minimum interval of 4 weeks can be accepted. For travellers aged ≥13 years, two doses with a minimum interval of 4 weeks may be recommended. MMRV is only licensed for children aged 1–12 years (see Measles, mumps and rubella) [4, 120].

In Canada, varicella immunisation is part of the routine schedule for all individuals aged >12 months. Serological testing for the presence of varicella antibodies is recommended for all unvaccinated adults since many will be immune through childhood exposure [7].

Herpes zoster

In the US, Herpes zoster vaccine (Zostavax) is routinely recommended as a single dose for adults aged >60 years for the prevention of herpes zoster, irrespective of whether they have had previous infection with varicella or herpes zoster. Although it is not recommended for those who have received varicella vaccine, providers do not need to enquire about having had the vaccine prior to Herpes zoster vaccination. It is a subcutaneous live vaccine consisting of the same attenuated Oka/Merck strain of varicella virus used in varicella vaccines but at a much higher strength (>14x stronger). Such a potent varicella vaccine is required to induce an adequate

immune response in adults who are probably already varicella seropositive due to natural exposure or previous varicella vaccination but who have reduced cellular immunity [4, 120]. The primary schedule consists of a single dose. Although it is currently thought to offer protection for at least 4 years, the understanding of the duration of protection is evolving. The overall efficacy was 61.1% for preventing zoster, 65.5% among those 60–69 years of age and 55.4% among those 70 and older. It has an efficacy of approximately 64% in those aged 60 years and 18% in those aged >80 years [121]. It is not recommended for the prevention of varicella. Side effects associated with the vaccine include localised pain and erythema, headache and myalgia [4].

Herpes zoster vaccination is not part of the Canadian routine immunisation schedule.

Australian and New Zealand travel immunisation guidelines

The travel immunisation guidelines and recommendations from Australia and New Zealand share many similarities with each other, and with the national guidelines of the UK and the international guidelines of the WHO. This section reviews these guidelines with specific reference to the main differences.

Table 14.4 shows the routine and travel specific vaccines as recommended at the time of writing in Australia. The Department of Health and Ageing publishes more detailed national guidelines in the Australian Immunisation Handbook www.health.gov.au/internet/immunise/publishing.nsf/content/handbook-home. Detailed immunisation guidelines for New Zealand are published by the Ministry of Health in the New Zealand Immunisation Handbook www.moh.govt.nz/moh.nsf/indexmh/immunisation-handbook-2011.

Principal differences

Certain populations living in Australia and New Zealand are at increased risk from vaccine-preventable infectious diseases arising from their poorer living conditions and reduced access to healthcare. This includes the Aboriginal and Torres Strait Islander people, especially those living in Queensland, the Northern Territory, Western Australia and South Australia, and Màori and Pacific Island people living in New Zealand. Additional vaccines are recommended as part of their routine immunisation schedules [122, 123].

The routine childhood immunisation programme in New Zealand is slightly different from that in Australia as it starts at 6 weeks of age with a dose of Infanrix-hexa and 10-valent pneumococcal conjugate (Synflorix), providing protection against diphtheria, tetanus, pertussis, polio, hepatitis B, Hib and pneumococcal infection [123, 124].

Hepatitis A

In Australia, hepatitis A vaccine forms part of the routine immunisation schedule in Aboriginal and Torres Strait Islander children aged 12–24 months from high-risk areas [124]. Travellers born before 1950 should be screened for pre-existing natural immunity before vaccination, and travellers living in endemic areas or who have a past medical history of jaundice should also have their hepatitis A antibody status checked before vaccination [124].

Hepatitis A vaccination is not otherwise part of the routine childhood immunisation programme in Australia or New Zealand but is recommended for all travellers aged >1 year travelling to moderately to highly endemic countries, including all developing countries [123, 124].

Hepatitis B

In Australia, universal childhood hepatitis B immunisation has been part of the routine childhood immunisation programme since 2000. A four-dose schedule is recommended if the first dose is administered within the first week of life. A three-dose schedule is recommended for all older children aged <18 years and all adults at increased risk of hepatitis B or severe infection [122]. Booster doses are not considered necessary for those who have completed the full course. Australian guidelines state that: 'as they could be exposed to risk during unplanned medical procedures all travellers intending to spend a month or more in Central and South America, Africa, Asia and Oceania should be vaccinated against hepatitis B'. This recommendation is somewhat different to the WHO and CDC recommendations. As research has shown a significant level of potential exposure and an unplanned medical procedure could occur at any time during travel, so many travel health practitioners would recommend hepatitis B vaccination to short-term travellers as well as those covered by the recommendation in the Immunisation Handbook [124–126].

In New Zealand, hepatitis B is also part of the routine schedule but consists of three doses commencing at 6 weeks of age [123].

Hib

In Australia, the routine infant immunisation schedule consists of three doses of a PRP-T Hib-containing vaccine (Hiberix and Infanrix hexa) administered at 2, 4 and 6 months, with a fourth booster dose at 12 months. PRP-OMP Hib containing vaccines (PedvaxHIB and COMVAX), consist of PRP polysaccharide Hib antigens conjugated to a meningococcal group B outer membrane protein (OMP). Such conjugate Hib vaccines are more immunogenic in infants

than PRP Hib vaccines conjugated with tetanus (PRP-T) or diphtheria toxins (PRP-D) or PRP polysaccharide Hib vaccines (unconjugated). These are the preferred Hib-containing vaccines for use in Aboriginal and Torres Strait Islander infants in areas of increased risk as a two-dose schedule at 2 and 4 months of age with a third booster dose at 12 months of age to provide more rapid protection [122].

Influenza

In Australia, annual influenza immunisation is encouraged for everyone aged 6 months or older but influenza immunisation is only funded by the government for all adults aged >65 years, all Aboriginal and Torres Strait Islander individuals aged >15 years, all individuals aged >6 months with chronic medical conditions, and pregnant women [122].

In New Zealand, influenza immunisation is funded for all adults aged >65 years and for younger people (from 6 months to 64 years) at increased risk of influenza complications [123].

Japanese encephalitis

Japanese encephalitis is part of the routine childhood immunisation schedule in the Torres Strait Islands of Australia from 12 months of age [124, 127]. Those visiting the Torres Strait Islands for a month or more during the wet season (December to May) are also advised to be vaccinated.

Meningococcoccal meningitis

Meningococcal disease is present worldwide, with some serogroups being more prevalent and responsible for epidemics in certain countries than in others. In the US, meningococcal serogroups A and Y are prevalent and both quadrivalent polysaccharide and conjugate vaccines are available. In Australia, Canada and the UK, serogroup C is more prevalent and meningococcal conjugate group C vaccines form part of the routine immunisation schedules. In Australia, meningococcal group B is the predominant cause of disease in the <5 years age group [124].

In Australia, a single dose of meningococcal C conjugated vaccine is recommended for all children aged 12 months. Vaccination before this age is not recommended unless there are specific chronic medical problems. A single dose of quadrivalent meningococcal polysaccharide vaccine has been the recommended travel vaccine for travellers aged >2 years but two quadrivalent conjugated vaccines are now available (Menveo and Menactra) [124].

Several meningococcal polysaccharide vaccines are available in New Zealand, including a monovalent group A vaccine (Menomune-A), a bivalent group A and C vaccine (Mencevax), and two quadrivalent group A, C, Y and W135 vaccines (Menomune ACYW-135 and MENCEVAX ACWY). Normally a quadrivalent polysaccharide vaccine is used when protection against one or all of the four contained quadrivalent groups is required. It is the recommended vaccine for travellers including to the Hajj and the meningitis belt of sub-Saharan Africa, for meningitis outbreaks in New Zealand, and for individuals with certain chronic medical conditions including individuals with splenic dysfunction and immunosuppression. The primary schedule consists of a single dose with boosters every 2–3 years for ongoing protection [123].

Two meningococcal conjugate C vaccines are licensed in New Zealand (Meningitec and NeisVac-C). The meningococcal A, C, Y, W135 quadrivalent conjugate vaccine Menactra is also available now in New Zealand. The meningococcal C conjugate vaccine is only recommended for young adults in their first year of hostel accommodation and close contacts of confirmed cases, but is only funded for a community programme to control an outbreak of group C disease [123].

Meningococcal serogroup B infection accounts for a large proportion of disease worldwide (including in the UK). At present no vaccine is available in most parts of the world because the meningococcal serogroup B polysaccharide has a very similar structure to neonatal neural cell surface antigens, induces a poor immune response, and vaccination may induce autoimmunity [128].

A meningococcal epidemic primarily associated with the meningococcal group B (B:4:P1.7b,4) strain was prevalent in New Zealand from 1991 to 2007. The epidemic disproportionally affected Màori and Pacific Island people. Meningococcal serogroup B outer membrane proteins (OMP) and outer membrane vesicles (OMV) are more immunogenic than the polysaccharide antigens. Therefore a strain-specific serogroup B meningococcal outer membrane vesicle (OMV) inactivated vaccine called MeNZB was developed to provide protection against this epidemic strain [123]. The vaccination programme ceased in 2008 because of a decline in the incidence of group B disease and because the immune response to the vaccine was short lived [123].

Development of a safe meningococcal serogroup B vaccine is a priority. Meningococcal serogroup B OMP vaccines have also been developed in response to meningococcal serogroup B epidemics in Norway against the B:15:P1.7.16 strain and in Cuba against the B:4:P1.19.15 strain, demonstrating efficacies of between 57% and 87% [111]. The vaccines have a varying degree of efficacy between different strains of meningococcal B infection due to a wide variation in PorA proteins [128]. The vaccines are being modified to cover different strains prevalent is different regions of the world [2].

MMR

Australians born before 1966 may be considered naturally immune to measles. A single-dose measles vaccination schedule began in Australia in 1968. The two-dose MMR vaccination schedule was introduced in 1994. MMR (Priorix) is the only currently available vaccine though measles-mumps-rubella-varicella vaccines are expected. All unvaccinated travellers aged >9 months should be vaccinated, including women of child-bearing age [124]. Travellers born during or since 1966 should be encouraged to have a dose of MMR vaccine before embarkation if they do not have evidence of having had two doses of vaccine in the past [124].

In New Zealand, people born before 1969 are considered immune to measles and a second dose of MMR is recommended for travellers between 1969 and 1981 [123].

Pneumococcal disease

In Australia, 13-valent PCV (Prevenar) is part of the routine immunisation schedule for all Australian children aged <2 years. The 13-valent vaccine replaced the 7-valent in July 2011. A single dose of 23-valent PPV (Pneumovax 23) is also routinely recommended for Aboriginal and Torres Strait Islander children aged 18 to 24 months living in high risk-areas at least 2 months after the last dose of PCV. Two doses of 23-valent PPV are routinely recommended for all adults aged >65 years and all Aboriginal and Torres Strait Islander adults aged >50 years with a 5-year interval between the doses. An additional fourth dose of 7-valent PCV is recommended for travellers with chronic medical conditions aged <10 years followed by a booster dose of 23-valent PPV at 5 years of age or at least 2 months after the final 7-valent PCV dose [124].

While 10-valent PCV (Synflorix) forms part of the routine childhood immunisation schedule in New Zealand and 13-valent PCV is funded for high risk children aged less than 5 years, PPV is not part of the adult routine schedule, although it is recommended at 65 years of age with revaccination after 5 years [124].

Q fever

In Australia, Q fever vaccination is recommended for certain individuals aged >15 years working with livestock, including farmers, veterinarians and abattoir workers. Potential side effects include local erythema and pain (very common), headache, fever and, very rarely, a localised abscess. Pre-vaccination antibody serology testing and skin testing is important to identify travellers previously exposed to Q fever and who are at risk of a hypersensitivity reaction to the vaccine. It is contraindicated in travellers with positive serology, positive skin testing, known previous natural infection, or who are pregnant. Booster doses are not recommended [122].

Rabies

Australian recommendations for rabies vaccination are similar to those of the UK. Cases of rabies in the local population in Bali have increased awareness of rabies as a risk to Australian travellers. Two cases of a fatal rabies-like illness caused by Australian bat lyssavirus (ABL) infection have occurred in people handling bats, and all species of Australian bats are considered to be potentially infected. The pre- and post-exposure schedule for use of rabies vaccine and human rabies immune globulin is the same for ABL as for rabies. Intra-dermal administration has not been shown to be effective for ABL [124].

Rotavirus

Rotavirus is part of the routine immunisation schedule in Australia. It is recommended but not funded in New Zealand (*see* US and Canadian guidelines section).

Tetanus, diphtheria and pertussis

The recommended age for using lower instead of higher antigen-content diphtheria and pertussis-containing vaccines varies slightly between countries. In Canada, the US and New Zealand it is 7 years, in Australia 8 years, and in the UK 10 years of age.

In Australia, the primary schedule for travellers aged >8 years consists of the administration of one dose of dTap and two doses of Td. Routine 10-yearly tetanus boosters are no longer recommended once a traveller has received five doses of tetanus vaccines. A single booster of Td (or dTap if not previously administered as a booster dose) is recommended after 50 years of age at least 10 years following the previous dose of tetanus [122, 124]. However, travellers to countries where healthcare services are difficult to access are recommended to have a booster dose of dT if more than 10 years has elapsed since the last does, or dTap if not previously administered as a booster dose. In New Zealand, five doses of a tetanus-containing vaccine are also recommended but with two further booster doses with Td at 45 and 65 years of age [123].

In Australia, tetanus post-exposure prophylaxis is not recommended for fully immune travellers who have received three doses of tetanus vaccine with the last dose having been administered within the previous 5 years. Non-immune travellers should receive a dose of tetanus vaccine and complete the recommended immunisation schedule. Travellers

should also receive tetanus immunoglobulin if they are exposed to a tetanus-prone wound and have had fewer than three doses of tetanus vaccine previously [122].

Tuberculosis

In Australia, an approach similar to that used in the UK is adopted, targeting BCG immunisation for individuals at increased risk, such as Aboriginal and Torres Strait Islander neonates in regions of high TB incidence, including the Northern Territory, Northern Queensland, and some parts of Western Australia and South Australia. BCG vaccination may be considered in travellers aged <16 years, especially those aged less than 5 years where the evidence of benefit is strongest, who are tuberculin-negative and going to travel for more than 3 months to a country with a high TB incidence (≥100 per 100 000 population). All travellers aged >6 months should have a tuberculin skin test before having BCG vaccination [122].

BCG is most effective in preventing extra-pulmonary TB, which is most common in infants and young children. Thus in New Zealand, BCG vaccination is only recommended for children aged <5 years at significantly increased risk of TB exposure through household contact. This includes travellers aged <5 years who in their first five years will be living for three months or longer in a country with rates of TB ≥ 40 per 100,000 [123].

Typhoid

In Australia, the primary schedule with oral live typhoid vaccine consists of the administration of either three or four doses with booster doses either every 3 or 5 years respectively. A four-dose schedule provides slightly more protection than three doses [122]. Parenteral typhoid polysaccharide vaccine is also available.

Varicella

In Australia, varicella is part of the routine childhood immunisation programme at 18 months of age. All non-immune immunocompetent travellers especially non-pregnant women of child-bearing age and travellers with asymptomatic HIV infection should be vaccinated. Serological testing may be considered pre-vaccination in older children and adults, but this is not recommended routinely following vaccination. At present the primary immunisation schedule for travellers aged <14 years consists of a single dose only and it is anticipated that two doses will be recommended in future for all travellers, based on evidence from studies conducted in the US. Only monovalent varicella vaccines are currently available but it is likely that a combined MMRV vaccine will become available soon in both Australia and New Zealand [122].

Varicella is not part of the routine immunization schedule in New Zealand [123].

Varicella zoster

In Australia, vaccination against herpes zoster is recommended for adults aged 60 years and over (*see* US and Canadian guidelines section) [122].

Further reading

Department of Health (2007) *Immunisation Against Infectious Disease – 'The Green Book'*. The Stationery Office, London. www.dh.gov.uk/greenbook (accessed 17 March 2009).

Health Protection Agency (2005a) Core Curriculum for Immunisation Training, http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1204100466949?p=1153846674367 (accessed 26 March 2010).

Health Protection Agency (2005b) National Minimum Standards for Immunisation Training, http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1204100464376 (accessed 26 March 2010).

Health Protection Agency (2009) Immunisation Training, http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1204012992964?p=1204012992964 (accessed 26 March 2010).

Lymphoedema Framework (2006) *Best Practice for the Management of Lymphoedema. International Consensus*. MEP Ltd, London. http://www.mepltd.co.uk/download_pdfs/LF%20best%20practice%2006.pdf (accessed 26 March 2010).

Australian Government (2005) National Vaccine Storage Guidelines – Strive for 5. Appendix 6, http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/DF94731AD8CBF34ECA2575BD001C8129/$File/strive-4-five.pdf (accessed 26 March 2010

Centers for Disease Control and Prevention (2012) Yellow Book 2012 – Health Information for International Travel, http://wwwnc.cdc.gov/travel/page/yellowbook-2012-home.htm (10 January 2012).

Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) (2011) Recommendations and Guidelines: Advisory Committee on Immunisation Practices (ACIP), http://www.cdc.gov/vaccines/recs/acip/ (14 October 2011).

Centers for Disease Control and Prevention (2011) Recommended adult immunization schedule – United States, 2011. *MMWR Morb Mortal Wkly Rep* **60**(4), 1–4.

Centers for Disease Control and Prevention (2011) Recommended immunization schedules for persons aged 0–18 years – United States, 2011. *MMWR Morb Mortal Wkly Rep* **60**(5): 1–4.

Ministry of Health, New Zealand (2011) New Zealand Immunisation Handbook, www.moh.govt.nz/moh.nsf/indexmh/immunisation-handbook-2011 (accessed 4 April 2011).

Australian Government Department of Health and Ageing (2008) Australian Immunisation Handbook 9th edn, www.health.gov.au/internet/immunise/publishing.nsf/content/handbook-home (accessed 19 May 2011).

Australian Government Department of Health and Ageing (2011) Immunise Australia Program, www.immunise.health.gov.au (accessed 19 May 2011).

References

1. The World Health Organisation (2010) *The World Health Organisation International Travel and Health Book 2010*. WHO, Geneva. http://www.who.int/ith/en/ (accessed 11 June 2010).
2. Department of Health (2007) *Immunisation Against Infectious Disease – The Green Book*. The Stationery Office, London. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917 (accessed 11 June 2010).
3. Plotkin SA et al. (eds) (2008) *Vaccines*, 5th edn. WB Saunders Company, Philadelphia.
4. Centers for Disease Control and Prevention (2012) Yellow Book 2012 – Health Information for International Travel, http://wwwnc.cdc.gov/travel/page/yellowbook-2012-home.htm (accessed 18 August 2011).
5. American Academy of Pediatrics (2003) Active immunisation. In: Pickering LK (ed.) *Red Book: 2003 Report of the Committee on Infectious Diseases*, 26th edn, p. 33. American Academy of Pediatrics, Elk Grove Village, IL.
6. Khakoo GA and Lack G (2000) Recommendations for using MMR vaccine in children allergic to eggs. *Br Med J* **320**: 929–932.
7. The Public Health Agency of Canada (2006) The Canadian Immunisation Guide, http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-eng.php (accessed 24 January 2010).
8. Royal College of Paediatrics and Child Health (2002) *Immunisation of the Immunocompromised Child –Best Practice Statement*.
9. British HIV Association (2006) Immunisation guidelines for HIV-infected adults, www.bhiva.org/pdf/2006/Immunisation506.pdf (accessed 10 January 2010).
10. Hesseling AC *et al.* (2007) The risk of disseminated Bacille Calmette-Guerin (BCG) disease in HIV-infected children. *Vaccine* **25**(1): 14–18.
11. Kengsakul K *et al.* (2002) Fatal myeloencephalitis following yellow fever vaccination in a case with HIV infection. *J Med Assoc Thai* **85**(1): 131–134.
12. Tattevin P *et al.* (2004) Yellow fever vaccine is safe and effective in HIV-infected patients. *AIDS* **18**(5): 825–827.
13. Stanley S *et al.* (1996) Effect of immunization with a common recall antigen on viral expression in patients infected with human immunodeficiency virus type 1. *N Engl J Med* **334**: 1222–1230.
14. O'Brien W *et al.* (1995) Human immunodeficiency virus-type 1 replication can be increased in peripheral blood of seropositive patients after influenza vaccination. *Blood* **86**: 1082–1089.
15. Brichacek B *et al.* (1996) Increased plasma human immunodeficiency virus type 1 burden following antigenic challenge with pneumococcal vaccine. *J Infect Dis* **174**: 1191–1199.
16. Glesby M *et al.* (1996) The effect of influenza vaccination on human immunodeficiency virus type 1 load: a randomized, double-blind, placebo-controlled study. *J Infect Dis* **174**: 1332–1336.
17. Health Protection Agency (2005) Core Curriculum for Immunisation Training, http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1204100466949?p=1153846674367 (accessed 26 March 2010).
18. Health Protection Agency (2005) National Minimum Standards for Immunisation Training, http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1204100464376 (accessed 26 March 2010).
19. Health Protection Agency (2009) Immunisation Training, http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1204012992964?p=1204012992964 (Accessed 26 March 2010).
20. Chiodini J *et al.* (2001) *UK Guidance on Best Practice in Vaccine Administration*. Shire Hall Communications, London, p. 76.
21. The electronic Medicines Compendium (2010) Summary of Product Characteristics, http://emc.medicines.org.uk/default.aspx (accessed 1st January 2010).
22. Zuckerman JN (2001) The importance of injecting vaccine into muscle. *Br Med J* **322**(7282): 364.
23. Shaw FE Jr *et al.* (1989) Effect of anatomic injection site, age and smoking on the immune response to hepatitis B vaccination. *Vaccine* **7**(5): 425–430.
24. Brachman PS *et al.* (1962) Field evaluation of a human anthrax vaccine. *Am J Public Health Nations Health* **52**(4): 632–645.
25. Hill DR *et al.* (2006) Oral cholera vaccines: use in clinical practice. *Lancet Infect Dis* **6**: 361–373.
26. Wittlinger F *et al.* (1995) Risk of cholera among Western and Japanese travelers. *J Travel Med* **2**(3): 154–158.
27. World Health Organization (2010) Cholera vaccines: WHO position paper. *Wkly Epidemiol Rec* **13**(85): 117–128.
28. Zuckerman JN *et al.* (2007) The true burden and risk of cholera: implications for prevention and control. *Lancet Infect Dis* **7**(8): 521–530.
29. Lucas ME *et al.* (2005) Effectiveness of mass oral cholera vaccination in Beira, Mozambique. *N Engl J Med* **352**: 757–767.
30. Taylor DN *et al.* (2000) Two-year study of the protective efficacy of the oral whole cell plus recombinant B subunit cholera vaccine in Peru. *J Infect Dis* **181**: 1667–1673.
31. Clemens JD *et al.* (1990) Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up. *Lancet* **335**: 270–273.
32. Jelinek T and Kollaritsch H (2008) Vaccination with Dukoral against travelers' diarrhea (ETEC) and cholera. *Expert Rev Vaccines* **7**(5): 561–567.
33. Van Loon FP *et al.* (1996) Field trial of inactivated oral cholera vaccines in Bangladesh: results from 5 years of follow-up. *Vaccine* **14**(2): 162–166.
34. Clemens JD *et al.* (1988) Cross-protection by B subunit-whole cell cholera vaccine against diarrhea associated with heat-labile toxin-producing enterotoxigenic Escherichia coli: results of a large-scale field trial. *J Infect Dis* **158**(2): 372–377.
35. Peltola H *et al.* (1991) Prevention of travellers' diarrhoea by oral B-subunit/whole-cell cholera vaccine. *Lancet* **338**(8778): 1285–1289.
36. Koff RS (1998) Hepatitis A. *Lancet* **351**: 1643–1648.

37. Mutsch M et al. (2006) Hepatitis A virus infections in travelers, 1988–2004. *Clin Infect Dis* **42**(4): 490–497.
38. Askling HH *et al.* (2009) Hepatitis A risk in travelers. *J Travel Med* **16**(4): 233–238.
39. Van Damme P *et al.* (2003) Hepatitis A booster vaccination: is there a need? *Lancet* **362**: 1065–1071.
40. Van Damme P *et al.* (2004) Do we need hepatitis A booster vaccinations? *J Travel Med* **11**: 179–180.
41. Rendi-Wagner P *et al.* (2007) Persistence of seroprotection 20 years after primary hepatitis A vaccination in an unselected study population. *Vaccine* **25**: 927–931.
42. Zuckerman JN *et al.* (2005) Hepatitis A and B booster recommendations: implications for travelers. *Clin Infect Dis* **41**(7): 1020–1026.
43. Van Damme P *et al.* (2001) Long-term persistence of antibodies induced by vaccination and safety follow-up, with the first combined vaccine against hepatitis A and B in children and adults. *J Med Virol* **65**(1): 6–13.
44. Van Damme P and Van Herck K (2004) A review of the efficacy, immunogenicity and tolerability of a combined hepatitis A and B vaccine. *Expert Rev Vaccines* **3**(3): 249–267.
45. Ambrosch F *et al.* (1994) Clinical and immunological investigation of a new combined hepatitis A and hepatitis B vaccine. *J Med Virol* **44**(4): 452–456.
46. Joines RW *et al.* (2001) A prospective, randomized, comparative US trial of a combination hepatitis A and B vaccine (Twinrix) with corresponding monovalent vaccines (Havrix and Engerix-B) in adults. *Vaccine* **19**(32): 4710–4719.
47. Zuckerman JN *et al.* (2000) Rapid protection against hepatitis A and hepatitis B following an accelerated schedule of a combined hepatitis A/B vaccine. *Antivir Ther (Lond)* **5**(1): 8.
48. Nothdurft HD *et al.* (2002)) A new accelerated vaccination schedule for rapid protection against hepatitis A and B. *Vaccine* **20**(7–8): 1157–1162.
49. Connor BA *et al.* (2007) Rapid and sustained immune response against hepatitis A and B achieved with combined vaccine using an accelerated administration schedule. *J Travel Med* **14**(1): 9–15.
50. Zuckerman J (2003) The place of accelerated schedules for hepatitis A and B vaccinations. *Drugs* **63**(17): 1779–1784.
51. Steffen R *et al.* (1987) Health problems after travel to developing countries. *J Infect Dis* **56**(1): 84–91.
52. Bush LM *et al.* (1991) Evaluation of initiating a hepatitis B vaccination schedule with one vaccine and completing it with another. *Vaccine* **9**: 807–809.
53. Asboe D *et al.* (1996) Hepatitis B vaccination schedules in genitourinary medicine clinics. *Genitourin Med* **72**(3): 210–212.
54. Bock HL *et al.* (1995) Accelerated schedule for hepatitis B immunisation. *J Travel Med* **2**: 213–217.
55. Nothdurft HD *et al.* (2004) Accelerated vaccination schedules provided protection against hepatitis A and B in last minute travelers. *J Travel Med* **11**: 260–261.
56. Zuckerman JN *et al.* (2003) Vaccination options for last-minute travellers in need of travel-related prophylaxis against hepatitis A and B and typhoid fever: a practical guide. *Travel Med Infect Dis* **1**(4): 219–226.
57. British Medical Association, Royal Pharmaceutical Society of Great Britain, Royal College of Paediatrics and Child Health, and Neonatal and Paediatric Pharmacists Group (2011) British National Formulary for Children 2011. BMJ Group, Pharmaceutical Press, and RCPCH Publications Ltd.
58. Zuckerman JN (2006) Protective efficacy, immunotherapeutic potential, and safety of hepatitis B vaccines. *J Med Virol* **78**(2): 169–177.
59. Hessel L and West DJ (2002) Antibody responses to recombinant hepatitis B vaccines. *Vaccine* **20**(17–18): 2164–2165.
60. André FE (1989) Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine. *Am J Med* **87**(3A): 14S–20S.
61. Poorolajal J *et al.* (2010) Long-term protection provided by hepatitis B vaccine and need for booster dose: a meta-analysis. *Vaccine* **28**(3): 623–631.
62. Roome AJ *et al.* (1993) Hepatitis B vaccine responsiveness in Connecticut public safety personnel. *JAMA: J Am Med Assoc* **270**(24): 2931–2934.
63. Smith JS *et al.* (2007) Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer* **121**(3): 621–632.
64. Lacey CJ *et al.* (2006) Chapter 4: burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. *Vaccine* **24**(3): S3/35–S3/41.
65. Harper DM *et al.* (2006) Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet* **367**(9518): 1247–1255.
66. Barr E and Tamms G (2007) Quadrivalent human papillomavirus vaccine. *Clin Infect Dis* **45**(5): 609–607.
67. Marti F *et al.* (2008) Influenza vaccine: a travelers' vaccine? *Expert Rev Vaccines* **7**(5): 679–687.
68. Freedman DO and Leder K (2005) Influenza: changing approach to prevention and treatment in travelers. *J Travel Med* **12**: 36–44.
69. Fleming DM *et al.* (1995) Study of the effectiveness of influenza vaccination in the elderly in the epidemic of 1989/90 using a general practice database. *Epidemiol Infect* **115**: 581–589.
70. Bridges CB *et al.* (2000) Effectiveness and cost-benefit of influenza vaccination of healthy working adults: a randomized controlled trial. *JAMA: J Am Med Assoc* **284**(13): 1655–1663.
71. Govaert TM *et al.* (1994) The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *JAMA: J Am Med Assoc* **272**(21): 1661–1665.
72. Jamieson D *et al.* (2009) H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* **374**(9688): 451–458.
73. Hancock K *et al.* (2009) Cross-reactive antibody responses to the 2009 pandemic influenza virus. *N Engl J Med* **361**: 1945–1952.
74. Schonberger LB *et al.* (1979) Guillain-Barre syndrome following vaccination in the national influenza immunization program, United States, 1976–1977. *Am J Epidemiol* **110**(2): 105–123.
75. Wittesjö B *et al.* (1995) Japanese encephalitis after a 10-day holiday in Bali. *Lancet* **345**(8953): 856–857.
76. Shlim DR and Solomon T (2002) Japanese encephalitis vaccine for travelers. Exploring the limits of risk. *Clin Infect Dis* **35**: 183–188.

77. Health Protection Agency (2010) National Travel Health Network and Centre, http://www.nathnac.org/ (accessed 19 January 2010).
78. Jelinek T (2009) Ixiaro: a new vaccine against Japanese encephalitis. *Expert Rev Vaccines* **8**(11): 1501–1511.
79. Miller E *et al.* (2001) Idiopathic thrombocytopenic purpura and MMR vaccine. *Arch Dis Child* **84**(3): 227–229.
80. Seagroatt V (2005) MMR vaccine and Crohn's disease: ecological study of hospital admissions in England, 1991 to 2002. *Br Med J* **330**(7500): 1120–1121.
81. Farrington CP *et al.* (2001) MMR and autism: further evidence against a causal association. *Vaccine* **19**(27): 3632–3635.
82. Redd SC *et al.* (2004) Comparison of vaccination with measles-mumps-rubella at 9, 12 and 15 months of age. *J Infect Dis* **189**(1): S116–S122.
83. Harling R *et al.* (2005) The effectiveness of the mumps component of the MMR vaccine: a case control study. *Vaccine* **23**(31): 4070–4074.
84. Morse D *et al.* (1994) Outbreak of measles in a teenage school population: the need to immunize susceptible adolescents. *Epidemiol Infect* **113**(2): 355–365.
85. Teyssou R and Muros-Le Rouzic E (2007) Meningitis epidemics in Africa: a brief overview. *Vaccine* **25**(1): A3–A7.
86. Al-Mazrou Y *et al.* (2005) Serologic responses to ACYW135 polysaccharide meningococcal vaccine in Saudi children under 5 years of age. *Infect Immun* **73**(5): 2932–2939.
87. US Food and Drug Administration (2010) Vaccines Licensed for Immunization and Distribution in the US with Supporting Documents, http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093830.htm (accessed 10 June 2010).
88. Pace D (2009) MenACWY-CRM, a novel quadrivalent glycoconjugate vaccine against Neisseria meningitidis for the prevention of meningococcal infection. *Curr Opin Mol Ther* **11**(6): 692–706.
89. Pace D (2009) Quadrivalent meningococcal ACYW-135 glycoconjugate vaccine for broader protection from infancy. *Expert Rev Vaccines* **8**(5): 529–542.
90. Ramsay ME *et al.* (2001) Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. *Lancet* **357**(9251): 195–199.
91. Mangtani P *et al.* (2003) Efficacy of polysaccharide pneumococcal vaccine in adults in more developed countries: the state of the evidence. *Lancet Infect Dis* **3**: 71–78.
92. Jackson LA *et al.* (2003) Effectiveness of pneumococcal polysaccharide vaccine in older adults. *N Engl J Med* **348**(18): 1747–1755.
93. Black S *et al.* (2002) Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. *Pediatr Infect Dis J* **21**(9): 810–815.
94. Nicholson KG (1990) Modern vaccines. Rabies. *Lancet* **335**(8699): 1201–1205.
95. Brookes SM *et al.* (2005) Rabies human diploid cell vaccine elicits cross-neutralising and cross-protecting immune responses against European and Australian bat lyssaviruses. *Vaccine* **23**(32): 4101–4109.
96. Ward JI *et al.* (2005) Efficacy of an acellular pertussis vaccine among adolescents and adults. *N Engl J Med* **353**(15): 1555–1563.
97. Blatter M *et al.* (2009) Immunogenicity and safety of a tetanus toxoid, reduced diphtheria toxoid and three-component acellular pertussis vaccine in adults 19–64 years of age. *Vaccine* **27**(5): 765–772.
98. Chen RT *et al.* (2000) Ukraine, 1992: first assessment of diphtheria vaccine effectiveness during the recent resurgence of diphtheria in the Former Soviet Union. *J Infect Dis* **181**(1): S178–S183.
99. Ritz N *et al.* (2008) To BCG or not to BCG? Preventing travel-associated tuberculosis in children. *Vaccine* **26**(47): 5905–5910.
100. Rodrigues LC *et al.* (1993) Protective effect of BCG against tuberculous meningitis and military tuberculosis: a meta-analysis. *Int J Epidemiol* **22**: 1154–1158.
101. Colditz GA *et al.* (1994) Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA: J Am Med Assoc* **271**(9): 698–702.
102. Connor BA and Schwartz E (2005) Typhoid and paratyphoid fever in travellers. *Lancet* **5**: 623–628.
103. Levine MM *et al.* (1999) Duration of efficacy of Ty21a, attenuated Salmonella typhi live oral vaccine. *Vaccine* **17**(2): S22–S27.
104. Acharya IL *et al.* (1987) Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of Salmonella typhi. A preliminary report. *N Engl J Med* **317**(18): 1101–1104.
105. Klugman KP *et al.* (1996) Immunogenicity, efficacy and serological correlate of protection of *Salmonella typhi* Vi capsular polysaccharide vaccine three years after immunization. *Vaccine* **14**(5): 435–438.
106. Mandal BK *et al.* (1998) Adult susceptibility to varicella in the tropics is a rural phenomenon due to the lack of previous exposure. *J Infect Dis* **178**: S52–S54.
107. Annunziato PW and Gershon AA (2000) Primary vaccination against varicella. In: Arvin AM and Gershon AA (eds) *Varicella-Zoster Virus*, pp. 460–477. Cambridge University Press, Cambridge.
108. Ferson MJ (2001) Varicella vaccine in post-exposure prophylaxis. *Commun Dis Intell* **25**(1): 13–15.
109. Marfin AA *et al.* (2005) Yellow fever and Japanese encephalitis vaccines: indications and complications. *Infect Dis Clin North Am* **1**: 151–168.
110. McMahon AW *et al.* (2007) Neurologic disease associated with 17D-204 yellow fever vaccination: a report of 15 cases. *Vaccine* **25**(10): 1727–1734.
111. Zuckerman JN and Jong EC (2010) *Travelers' Vaccines*, 2nd edn. PMPH-USA, Shelton.
112. Lindsey NP *et al.* (2008) Adverse event reports following yellow fever vaccination. *Vaccine* **26**(48): 6077–6082.
113. Barwick R (2004) History of thymoma and yellow fever vaccine. *Lancet* **364**: 936.
114. Hayes EB (2007) Acute viscerotropic disease following vaccination against yellow fever. *Trans R Soc Trop Med Hyg* **101**: 967–971.
115. Khromava AY *et al.* (2005) Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. *Vaccine* **23**(25): 3256–3263.
116. Monath TP *et al.* (2002) Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX™ and yellow

fever-VAX®) in a Phase III multicenter, double-blind clinical trial. *Am J Trop Med Hyg* **66**: 533–541.
117. Barrett AD and Teuwen DE (2009) Yellow fever vaccine – how does it work and why do rare cases of serious adverse events take place? *Curr Opin Immunol* **21**(3): 308–313.
118. Wilder-Smith A (2009) Meningococcal vaccines: a neglected topic in travel medicine? *Expert Rev Vaccines* **8**(10): 1343–1350.
119. Poland GA (2010) Prevention of meningococcal disease: current use of polysaccharide and conjugate vaccines. *Clin Infect Dis* **50**(S2): S45–S53.
120. Czajka H *et al.* (2009) A combined measles, mumps, rubella and varicella vaccine (Priorix-Tetra): immunogenicity and safety profile. *Vaccine* **27**(47): 6504–6511.
121. Oxman *et al.* (2005) A vaccine to prevent herpes zoster and post-herpetic neuralgia in older adults. *NEJM* **352**(22): 2271–2284.
122. Australian Government Department of Health and Ageing (2011) Immunise Australia Program, www.immunise.health.gov.au (accessed 19 August 2011).
123. Ministry of Health, New Zealand (2011) New Zealand Immunisation Handbook, www.moh.govt.nz/moh.nsf/indexmh/immunisation-handbook-2011 (accessed 19 August 2011)
124. Australian Government Department of Health and Ageing (2008) Australian Immunisation Handbook 9th edn, www.health.gov.au/internet/immunise/publishing.nsf/content/handbook-home (accessed 19 August 2011).
125. Streeton CL and Zwar N (2006) Risk of exposure to hepatitis B and other blood-borne viruses among Australians who travel abroad. *J Travel Med* **13**: 345–350.
126. Leggat P *et al.* on behalf of the Travel Health Advisory Group (2009) Hepatitis B risks and immunisation coverage amongst Australians travelling to Southeast Asia and East Asia. *Travel Med Infect Dis* **7**: 344–349.
127. Hanna JN *et al.* (1996) An outbreak of Japanese encephalitis in the Torres Strait, Australia, 1995. *Med J Aust* **165**(5): 256–260.
128. Granoff DM (2010) Review of meningococcal group B vaccines. *Clin Infect Dis* **50**(S2): S54–S65.

Chapter 15 Returned travellers

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Introduction

The exponential growth of international travel means that healthcare workers regularly see patients who have recently travelled abroad or outside their local area of residence. In 2011, the numbers of international tourist arrivals increased by 4.6 percent to 983 million [1]. The travel-related problem is often a minor cosmopolitan illness – we have probably all suffered from respiratory infections acquired while attending professional conferences, and international airline passengers routinely expect to have swollen feet and jet lag when they reach their destinations. However, the increasingly adventurous nature of many tourists and the continued emergence of new infection risks in all parts of the world make it essential that travel-related illness is both considered and managed appropriately. Unfortunately, a travel history is rarely elicited in most day-to-day consultations, leading to delay in considering and making a relevant diagnosis [2].

The purpose of this chapter is to outline an approach to the diagnosis and management of travel-related disease, concentrating on infections imported from less economically advantaged areas of the world to the more affluent nations. The framework for this approach is careful history taking, relevant examination and investigation.

The travel 'expert' will need to have a detailed understanding of the health problems most likely to affect different groups of travellers, coupled with current knowledge of the illnesses prevalent in areas visited by the patient. Synthesis of this knowledge with the clinical presentation of the patient should enable a sensible syndromic differential diagnosis to be made, allowing for an appropriate management plan to be developed. Our aim is to highlight key decision points in these steps, using worked examples and illustrative tables and algorithms. The emphasis is on imported infections that are most 'important', either by virtue of being common and amenable to treatment, or because of their public health importance on the rare occasions that they are seen. Greater detail about individual infections is found in other chapters of this book or in major textbooks of infection and tropical medicine (*see* Further reading).

Patients who are suspected in community practice of having a specific illness, such as malaria, HIV infection or imported parasitosis, will usually need to be referred to hospital or clinic-based specialists for further investigation and management. In these cases the priorities are to prevent immediate morbidity and mortality and to minimise any public health risks to the general population or to healthcare workers. In some groups of travellers, post-travel health screening may be appropriate in either a general practice setting or in specialist clinics, and we discuss issues relating to screening at the end of the chapter.

History

A precise and detailed travel history is essential. This should include questions about all previous international travel as well as the most recent trip, as valuable clues may be missed.

Case history

A 45-year-old man presented to the emergency room late in the evening with fever, dizziness and diarrhoea. He had returned from a 1-week holiday in Greece 6 days previously, and had visited India 6 months before. He had high fever, hypotension, mild renal failure and marked thrombocytopenia. His blood film was not examined until the following morning, when it showed 17% parasitaemia with *Plasmodium falciparum* malaria and treatment with quinine was started. Further questioning revealed that he had been working in West Africa for 2 months until he joined his wife in Greece.

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Table 15.1 Initial questions for the travel history

When

- When did you last travel outside the country? Exact dates of departure and return
- When did you last travel away from home? When did you travel before that?
- When did you first get ill? Exact dates if possible

Where

- Where were you born?
- Where exactly did you go on this trip? Precise location, not just country or continent
- Where did you stop along the way?

Why

- Why did you go abroad? Business, tourism, visiting family, etc.

What

- What health problems did you already have before travel?
- What method of transport did you use?
- What did you do there? Risk activities – freshwater contact, etc.
- What precautions did you take before you went? List immunisations, etc.
- What precautions did you take while there? Quantify adherence to safe eating, safe sex, antimosquito measures

Who

- Who else went with you?
- Who else got ill?

Type of traveller

The key initial questions to be asked when taking the travel history are summarised in Table 15.1. These can be modified depending on the type of traveller and the likely risk behaviour and possible exposure to disease. Short-term casual tourists to coastal Kenya are at risk of acquiring malaria even when taking chemoprophylaxis, but are less likely to acquire legionella infection, which is more typically associated with air-conditioned hotels in Spain, Turkey or other 'western' settings. The younger, adventurous overland traveller is more likely to be exposed to pathogens in the environment and to their vectors and to take risks with their diet, daily activities and interpersonal behaviour. For example, the incidence of hepatitis A is estimated to be 2–3/1,000 in 'ordinary' travellers and 20/1,000 in backpackers [3, 4]. Expatriates working overseas have varying levels of access to preventive healthcare and often disregard advice they have received, especially about malaria prophylaxis. The risk of acquiring some infections also increases with the amount time spent overseas. Attack rates of malaria in British travellers to West Africa increased from 61/100,000 in those travelling for 1 week to 4899/100,000 in those travelling for 6–12 months [5].

Immigrants present their own problems, which are discussed in greater detail in Chapter 29. Within this broad group there will be several subdivisions according to the reason for immigration. Refugees and other displaced persons are likely to import illnesses that are endemic within the communities from which they originate, and may also have been exposed to physical deprivation, malnutrition and abuse in reception camps during their travels. They are also more likely to have psychological abuse and stressors. They may present with a combination of background endemic illness, as well as emerging or epidemic infection, often superimposed on a different cultural approach to health care usage and complicated by the psychosocial distress of the upheavals in their lives. Many countries now have their own policies with respect to screening for various infectious diseases such as tuberculosis, hepatitis B, hepatitis C, Human Immunodeficiency Virus (HIV), Chagas' disease and various gastrointestinal parasites.

Members of these groups visiting friends or relatives at 'home' (VFR) are less likely to be aware of, or to take, preventive precautions advised for expatriate tourists or visitors [6], but will have lost the immunity to endemic disease that is acquired by constant exposure. Illness in this group is relatively overrepresented in summary statistics of imported disease.

Individual host factors influence both susceptibility to disease and the mode of presentation. Patients should be asked about background illness, such as ischaemic heart disease, chronic respiratory illness, renal disease, immobility due to arthritis or other disability and prior psychiatric illness. Diabetes is thought to predispose the individual to many infections and is an important risk factor for acquiring melioidosis. Pregnant women are more likely to have recrudescence of malaria or to have more severe clinical illness due to malaria. Ill children present with fewer localising features of illness than adults and are more likely to have fever with gastrointestinal infections. Patients who have had a splenectomy are at increased risk of bacterial infections, such as invasive pneumococcal disease, and blood parasites, particularly malaria and babesiosis. Pre-existing anaemia will exacerbate the presentation of many acute infections and sickle cell disease specifically carries risks of both pneumococcal disease and malaria, as well as crises induced by travelling to high altitude or by dehydration. Smoking increases the risk of pneumococcal infection, meningococcal disease and severe Legionnaires' disease. Excess alcohol consumption is associated with increased risk taking in general, and particularly with a high risk of trauma, drowning incidents, traffic accidents and increased sexual risk

behaviour. Patients with cirrhotic liver disease have high morbidity from many bacterial infections and from viral infections causing hepatitis. Patients with immunosuppressive disorders, particularly HIV-related problems and those on chemotherapy for cancer or after transplants, are more susceptible to a wider variety of pathogens than the immunocompetent person.

Drugs and vaccinations

A full immunisation history is essential as it will alter the approach to diagnosis in ill patients. This includes appropriate vaccination according to region of visit as well as updated childhood immunisation.

Case history

A 36-year-old man returned from the Ivory Coast to Germany with a febrile illness, jaundice and bleeding diathesis. He was initially thought to have Lassa fever and was nursed accordingly until his death. The cause of death was determined to be yellow fever, which had been thought unlikely as the patient had claimed, incorrectly, to have been immunised against yellow fever [7].

Yellow fever vaccination is extremely effective, but cases continue to be imported to Europe and North America from both Africa and South America by travellers who have not been immunised [8]. Active immunisations against hepatitis A and B are both more than 90% effective, whereas currently licensed vaccines against typhoid only have 70% or less protective efficacy. The effectiveness of antimosquito bite measures and antimalarial chemoprophylaxis is variable and highly dependent on adherence by travellers.

Concurrent medication for underlying illness may cause or exacerbate symptoms. For example, aspirin taken to prevent travel-related thrombosis may cause or worsen gastrointestinal bleeding, and diuretic therapy increases the dehydration associated with diarrhoeal illness. Mouth ulcers are common in patients taking proguanil; chloroquine can exacerbate psoriasis; prophylactic doxycycline is associated with vaginal thrush and with photosensitive rashes; and mefloquine use has been linked with various neuropsychiatric effects [9].

Where did the patient visit?

This must include the locality as well as the countries visited. While many infections are cosmopolitan, their prevalence within a given country may be very localised. British travellers to North America will not be exposed to infections such as plague, tularaemia, hantavirus infection, Colorado tick fever or coccidioidomycosis if they visit New York, although these are all possibilities if they have been camping out in some of the southern states. Malaria is a significant hazard for travellers to Kenya but should not be a problem for those who stay in Nairobi, and similarly tourists to Thailand are unlikely to acquire malaria in Bangkok but might be at risk in rural areas. Travellers attending mass gatherings such as the yearly Hajj pilgrimage are exposed to a variety of risks, especially airborne infections such as meningococcal disease and influenza, and gastrointestinal infections [10]. The geographical distribution of the more common imported diseases is illustrated with cases in this chapter and in detail in other chapters in this book. Current information on established and emerging infections in different parts of the work is available from a number of websites (*see* Additional resources).

Healthcare workers need to be aware of the geography of the patterns of drug resistance of organisms as well as the distribution of the pathogens themselves. Many gastrointestinal pathogens such as *Shigella* and *Salmonella* species acquired overseas are resistant to commonly used antimicrobials [11, 12, 13]. *Salmonella typhi* from Asia and the Indian subcontinent, and *Mycobacterium tuberculosis* from many countries, exhibit multidrug resistance [14, 15]. Resistance of falciparum malaria to chloroquine is almost universal, while resistance to other antimalarials is more patchy in distribution (Chapter 10). Knowledge of these resistance patterns is essential when planning empirical therapy before the results of culture (and sometimes resistance testing) are available.

When did they travel and for how long?

A precise history of timing of travel is essential for comparison with the known incubation periods of specific illnesses, some of which are summarised in Table 15.2.

In the clinic consultation, it is rarely as easy as one might expect to correlate exposure dates with illness in individual patients. In this situation, incubation periods are most useful for excluding illness. For example, malaria does not present in travellers less than 8 days after arriving in a malarious area. Viral haemorrhagic fever can safely be excluded in a patient who has had possible exposure, but has left an endemic area more than 21 days before the onset of symptoms. In epidemic situations or outbreaks clearly related to a point source, knowledge of precise travel and exposure times is very helpful, such as locating a patient within a known outbreak of Legionnaires' disease on a cruise ship or in a specific hotel, or identifying a person as being part of a point source

Table 15.2 Sample incubation periods

Short (<10 days)	Medium (10–21 days)	Long (>21 days)	Very long
Amoebiasis (intestinal)	Amoebiasis	Amoebic liver abscess	AIDS/symptomatic HIV
Anthrax (pulmonary)	Arboviral infections (few)	Babesiosis	Amoebic liver abscess
Arboviral	Murray Valley fever	Bartonellosis	Chagas' disease
Chikungunya	Encephalitis	Brucellosis	Leprosy
Dengue fever	St Louis	Cytomegalovirus	Leishmaniasis
Japanese encephalitis	Tick-borne	Filariasis	Melioidosis
Yellow fever	Japanese	Hepatitis (A–E)	Neurocysticercosis
Babesiosis	Babesiosis	HIV infection (acute)	Schistosomiasis
Bacterial meningitis	Brucellosis	Infectious mononucleosis	Strongyloidiasis
Brucellosis	Cytomegalovirus	Leishmaniasis (visceral)	Tuberculosis
Campylobacter enteritis	Haemorrhagic fevers	Lyme disease	
Diphtheria	Congo–Crimean	Malaria (all species)	
Ehrlichiosis	Lassa fever	Melioidosis	
Fascioliasis (acute)	Marburg/Ebola	Q fever	
Haemorrhagic fevers	Hepatitis A, E	Rabies	
Argentinian	Histoplasmosis	Schistosomiasis (acute)	
Bolivian	Leptospirosis	Secondary syphilis	
Lassa	Loeffler syndrome	Toxocariasis	
Marburg/Ebola	Lyme disease	Trench fever	
Congo–Crimean	Malaria (all species)	Trypanosomiasis	
Influenza	Measles	African	
Legionnaires' disease	Melioidosis	(*T. b. gambiense*)	
Leptospirosis	Monkeypox	American	
Loeffler syndrome	Polio	Tuberculosis	
Lyme disease	Psittacosis	Typhoid	
Malaria (unusual)	Q fever		
Melioidosis	Rabies		
Monkeypox	Toxocariasis		
Necrotising enterocolitis	Toxoplasmosis		
Plague	Trichinosis		
Poliomyelitis	Trypanosomiasis		
Psittacosis	African		
Rabies	(*T. b. rhodesiense*)		
Rat-bite fever	American		
Relapsing fevers (borreliosis)			
Rotavirus			
Salmonella enterocolitis			
Shigellosis			
Streptococcal pharyngitis			
Toxigenic *Escherichia coli*			
Toxocariasis			
Trypanosomiasis (African, acute)			
Tularaemia			
Typhoid and paratyphoid			
Typhus			
African tick			
Flea-borne			
Louse-borne			
Mite-borne (scrub)			
Rocky mountain spotted fever			
Yersiniosis			

outbreak of food-borne salmonellosis at a wedding reception on the other side of the country. Such examples emphasise both the use of the travel history to inform the diagnosis of the patient and the need for rapid notification of suspected and confirmed diagnoses to the appropriate public health authorities or surveillance scheme, so that patterns of illness and outbreaks can be recognised and disseminated back to the healthcare community.

At the other end of the scale, diseases with long incubation periods may not be recognised as travel-related by either the patient or physician. Hepatitis B transmitted by tattoo during an overland trip through Asia might not cause illness until 6 months later. The increased risk of tuberculosis in immigrants persists for at least 5 years after arrival in Britain [16] and the clinical incubation period of symptomatic leprosy is several years [17]. We have seen patients with colonic bleeding due to schistosomiasis presenting for the first time 10 years after travel to Africa. Some infections can persist for many years, such as strongyloidiasis, which we still see in ex-prisoners of war who worked more than 60 years ago on the Thai–Burma railway during World War II [18]. Knowledge of the biology of the pathogen can also be integrated with the detailed travel history to recognise the limitation of investigation at different phases of the illness.

Case history

A 19-year-old student presented in Liverpool with a 4-week history of headache, fever and malaise, followed by a dry cough and a transient urticarial rash. He had fever and a peripheral eosinophil count of 2.4×10^9/l but appropriate examination of faeces and urine for parasites and schistosomal serology was negative. Acute schistosomiasis (Katayama fever) was diagnosed by the family practitioner, who was aware that the patient had been swimming in Lake Malawi 6 weeks previously with a group of students who had similar symptoms. We confirmed the clinical diagnosis and 6 weeks later his serology became positive, and scanty ova of *Schistosoma haematobium* were found.

Other students from the party had been investigated elsewhere in the country without a diagnosis being made, partly because the attending physicians failed to recognise that serology make take more than 2–3 months to become positive, and that conventional parasitological tests are negative during the acute phase of the illness.

Why did they travel and what did they do?

Some occupational groups are inevitably at greater risk of exposure to vectors and illness. Healthcare personnel are particularly prone to the risk of needlesticks and similar accidents, as well as dealing with patients with pathogens that can be spread by airborne droplets or by direct contact with body fluids and faeces. The difficulties in preserving high levels of risk avoidance in a rural hospital setting are all too common and emphasised by the tragic deaths of healthcare workers assisting patients with Ebola infection in Uganda [20] or Congo-Crimean haemorrhagic fever in South Africa, the Middle East and Pakistan. Tuberculosis has always been a problem for healthcare staff and remains a hazard for those working overseas in areas of high endemicity [21].

Other groups, such as veterinarians and agricultural workers, will be at increased risk of zoonotic infections such as brucellosis, Q fever and anthrax through contact with animals. Forestry workers, construction workers and other project workers may venture into forested or other rural ecosystems and be at risk of arthropod-borne diseases such as trypanosomiasis, onchocerciasis, loiasis, filariasis, rickettsial infection, leishmaniasis, *P. knowlesi* malaria and yellow fever.

Aid workers and others in refugee or school settings are at risk of acquiring diseases of overcrowding such as respiratory infections and meningococcal disease. Military personnel constitute a special group. Although they may have received adequate immunisation and advice on malaria prevention, the latter advice may not be heeded in difficult field conditions. Their activities may result in considerable exposure to a wide variety of soil-borne pathogens, for example hookworms and *Strongyloides* spp, as well as to arthropod-borne and food- and water-borne illnesses. Sexually transmitted diseases also continue to be a particular problem in military personnel and merchant seamen. Adventure travel is increasingly popular and individuals are travelling to more remote and exotic destinations. This pursuit may increase the likelihood of contact with unusual pathogens as well as the lack of adequate clean water.

Table 15.3 summarises some of the typical risks associated with different patterns of exposure behaviour.

Sexual history

The importance of taking an appropriate sexual history from travellers cannot be overemphasised. This poses problems in the busy practice, clinic or hospital setting but it is essential to include such enquiries as a matter of routine. A suitable excuse needs to be found to exclude parents, partners or friends who accompany the patient while this part of the history is taken. People go on holiday to have fun, and for many this includes new sexual experiences, often associated

Table 15.3 Specific exposures and tropical infections causing fever

Exposure	Infection or disease
Raw, undercooked or exotic foods	Enteric infections, hepatitis A or E, trichinosis, listeriosis, paragonimus
Drinking untreated water, milk, cheese	Salmonellosis, shigellosis, hepatitis, brucellosis, giardiasis
Freshwater swimming	Schistosomiasis, leptospirosis
Soil exposure	Melioidosis, histoplasmosis, coccidioidomycosis
Caves	Marburg, histoplasmosis, rabies
Sexual contact	HIV, syphilis, hepatitis A or B, gonorrhoea, etc.
Insect bites	Malaria, dengue fever (mosquitoes); typhus, Crimean–Congo haemorrhagic fever, borreliosis, tularaemia (ticks); Chagas' disease (reduviid bugs); African trypanosomiasis (tsetse flies)
Animal exposure/bites	Rabies, Q fever, tularaemia, borreliosis, viral haemorrhagic fevers, plague, hantavirus, psittacosis, rat-bite fever
Exposure to infected persons	Viral haemorrhagic fevers, hepatitis, typhoid, meningococcaemia

After Humar and Keystone (1996) [19].

with high-risk partners. This is particularly true for young adults [22, 23, 24]. In one British study, 74% of male migrant tourism workers in a popular coastal resort had sex with tourists, almost half with more than four tourists, and only 40% of respondents had used a condom [25]. Teenagers are just as busy when visiting other European destinations, particularly those associated with the dance-music scene. In a study performed in Ibiza, over a third of 846 young adults attending music venues had taken recreational drugs, and 58% of males and 50% of females had at least one new sexual partner during their 1- to 2-week stay. Twenty-six per cent did not use condoms and 23% had more than one sexual partner [26]. Similar risk behaviour has been shown in expeditioners and in long-term expatriates [23], often associated with high levels of alcohol use.

The risk of acquiring sexually transmitted infection abroad is very high and includes 'traditional' infections such as gonorrhoea (often multidrug resistant), syphilis, chancroid and lymphogranuloma venereum [27]. The prevalence of HIV in sex workers in many cities and towns in India, Thailand and much of Africa exceeds 60% and is rapidly increasing in many other parts of the world, including the Eastern bloc countries, where syphilis has reached epidemic proportions [28].

Fifteen per cent of UK-born adults diagnosed in England, Wales and Northern Ireland between 2002 and 2010 acquired HIV infection abroad. Thailand, the USA and South Africa were the countries most commonly reported. As compared with UK-born adults acquiring HIV infection in the UK, those acquiring HIV infection abroad were significantly more likely to have acquired it heterosexually, to be of older age at diagnosis and to have reported sex with a commercial sex worker (5.6% vs. 1%, respectively) [29].

HIV remains the single most common and potentially lethal imported sexually transmitted infection, but advances in medical management have significantly improved the prognosis. Patients who have been at risk of infection require consent and testing for HIV and other sexually transmitted infections. This usually implies referral to a genitourinary medicine clinic for a full screen because sexually transmitted diseases may be asymptomatic in both men and women.

How did they go?

In addition to the behavioural and exposure risks already described in different groups of travellers, the mode of travel predisposes to specific medical problems. Immobility due to prolonged travel is likely to predispose to venous thrombosis and pulmonary embolism, especially in patients with pre-existing risk factors. It is possible that specific factors associated with air travel, such as low air pressure, hypoxia and dehydration, exacerbate this, but the evidence base is poor and few scientific data have been published to quantify such an increase in risk [30]. Venous thrombosis and pulmonary embolus should be considered in the differential diagnosis of recent travellers, particularly in those with leg pain, fever or dyspnoea.

In-flight medical emergencies affect about 1/11,000 passengers and comprise a full range of medical problems, some of which need further attention when the patient arrives, including the effects of overindulgence in alcohol [31, 32]. Recirculation of air leads to sharing of pathogens, and the transmission of influenza [33] and tuberculosis between air passengers is recorded. Although the risk of tuberculosis transmission is low and is limited to passengers near to the index case, it generates considerable concern [34, 35].

Passengers and crew on cruise ships are also exposed to conditions of crowding, and respiratory symptoms are the most common reason for consultation (29%) during cruises. Although tuberculosis transmission was a major occupational health risk in the Navy and merchant marine, it has not been reported as a risk for cruise ship passengers. Outbreaks of influenza are well described and several serious outbreaks of Legionnaires' disease have been reported on

cruise ships [36, 37]. Problems with gastroenteritis are also commonly recorded, including bacterial infections caused by pathogens such as *Shigella* spp, *Salmonella* spp and *Vibrio* spp. More devastating are the frequently recorded explosive outbreaks of small round structured viruses such as noroviruses and similar agents, particularly in an elderly population, although the majority of passengers so affected will be treated on ship and recover before returning to shore [38]. Expedition travel is less hazardous than one might expect. A recent review of 210 trips arranged by one company included 4077 participants over 42,482 days in the field. Out of a total of 1,564 incidents, 1,465 (94%] cases were of 'minor' injury or illness, 79 (5%] 'moderate', and 20 (1%] 'major' in severity [39]. Gastrointestinal upset was the commonest reported minor condition and severe acute mountain sickness the commonest major condition. In a similar questionnaire survey of 246 expedition leaders, 835 medical incidents occurred in 130,000 person-days of travel, and of 206 expedition participants treated by a doctor, only 10 saw their general practitioner and only five needed to see a hospital doctor after their return to the UK [40].

The patient who has not travelled

A key reason for identifying imported infection is to minimise the chance of onward transmission to the local population by appropriate treatment and isolation of the index case. One of the earliest examples of this was the 40-day (quarantine) period of detention offshore, introduced for ships arriving in Venice, Ragusa (Dubrovnik) and Rhodes in the 14th century to prevent the importation of plague. This has been brought back into public focus by the recent international spread of infections such as meningococcal infections following the Hajj and respiratory infections such as SARS and pandemic influenza. Specific guidelines have been produced for containment of specific pathogens that are rarely imported but are of public concern, such as the viral haemorrhagic fevers [41, 42]. Travel histories of relatives and friends should always be considered when dealing with patients with a potentially infectious disease, particularly in groups such as students or immigrants who have frequent contact with international travellers.

Case history

A 24-year-old woman of Indian ethnic origin was admitted to hospital in Liverpool with 1 week of illness typical of acute viral hepatitis. Both she and her husband (also of Indian ethnic origin) had been born and brought up in the UK. Her husband had returned from his first trip to India 2 months before, and had been managed at home with probable hepatitis starting 1 month before. She was confirmed as having hepatitis E, imported by her husband.

Hepatitis E is usually a travel related infection in Western countries, although endemic infection is increasingly recognized [43]. This case illustrates the importance of taking a good contact and travel history in all patients.

Travel histories should be relayed to diagnostic laboratories, so that the relevant tests are performed to diagnose exotic pathogens that might otherwise not be sought. This is also essential because of the potential risk of many pathogens to the laboratory workers themselves, including especially brucellosis, transmission of which is common in laboratories in endemic areas and is also a hazard when incorrectly identified samples are sent internationally [44]. Apart from exposure to airborne pathogens such as brucellosis, laboratory workers are at special risk from inoculation accidents involving exotic pathogens, such as malaria, trypanosomiasis and leishmaniasis, which will require urgent specialist advice [45]. Failure to diagnose the index infection can lead to tragic consequences in healthcare workers involved in needlestick incidents. Finally, the risk of transmission of imported infection by blood transfusion has long been recognised for malaria [46], but is now increasingly recognised for other pathogens such as American trypanosomiasis, which may also be transmitted perinatally [47].

Case history

A doctor in Sicily suffered a needlestick injury while attending a patient with fever imported from Africa. The patient's malaria was subsequently diagnosed and treated in London, but by then the doctor had died from undiagnosed malaria [48].

Exotic infections can travel with their vectors and the hazards of imported zoonotic infections have been highlighted by the recent epidemics of Rift Valley fever in the Yemen and Saudi Arabia, related to imported livestock [49]. Similar concerns accompany international movement of domestic pets; this is a particular issue for countries such as the UK that are currently rabies-free and whose regulations relating to pet movement are being relaxed, allowing exposure of animals to a variety of other infections as well as rabies, some of which have potential for spread to humans [50]. Exotic pathogens may be imported with other animals, such as psittacosis associated with a variety of birds, salmonellosis with reptiles and monkeypox in rodents [51].

Insect vectors survive travel despite regulations designed to hinder them, such as spraying vehicles moving out of the trypanosome belt in Africa, or spraying aeroplanes to kill mosquitoes. So-called 'airport malaria' affecting non-travellers has been reported from several countries that do not usually have local malaria transmission [52].

Table 15.4 Differing patterns of the clinical diagnosis in 6,957 returning travellers presenting with fever to GeoSentinel clinics around the world, according to where they had been [59].

	Fever[a]	Malaria	Dengue	No diagnosis	Respiratory	Diarrhoeal
Oceania	51	59	6	12	10	4
SS Africa	41	42	1	19	10	10
SE Asia	33	7	18	22	17	17
SC Asia	27	7	9	20	14	22
N Asia	24	1	0	26	39	11
N Africa	22	5	1	13	13	38

Figures are percentage of travellers returning from each region.
[a]Percentage of travellers to the area that had fever.

These imported hazards will only be considered by the healthcare worker who keeps an open mind and thinks laterally about the situation of the patient. This is not so easy in the growing number of cases of illness caused by pathogens imported with food, identification of which requires sophisticated public health surveillance mechanisms [53].

The patient with fever

The majority of serious imported infections present with fever as the predominant or major symptom, and it is essential that a timely diagnosis is made in such patients [19, 54]. Other common syndromes in returned travellers include respiratory disease, diarrhoeal disease and skin problems [55]. Earlier published studies on the diagnostic outcome of imported fever cases were hospital-based and subject to considerable referral bias. A typical report from the Hospital for Tropical Diseases in 1986 showed that 553 of 1,084 adults admitted with imported infection had fever and that 42% of these had malaria [56]. Subsequent local studies in Australia and the UK confirmed that approximately 40% of such hospitalised patients had malaria and that cosmopolitan, nonspecific illness was the second most common diagnosis, in addition to a substantial proportion of patients with no final diagnosis [57, 58]. A more global view is seen in the continuing Geosentinel studies, although these are still biased towards travellers attending specialist clinics. Among 6,957 returned travellers whose main symptom was fever, the most likely causes depend on where they have been – malaria is the most likely cause after travel to sub Saharan Africa, but other infections such as dengue are more likely after visiting South Asia (Table 15.4) [57, 58, 59].

The patterns of imported illness in children resemble those in adults, but children are proportionally more likely than adults to present early (within 7 days) after travel and to require hospitalisation [60, 61]. Diarrhoeal disease is often more prominent in children, along with febrile illness, followed by respiratory and cutaneous problems. Malaria remains the most common imported infection recognised in children in the UK [62] and is even more common in VFR groups than adults [63, 64].

Table 15.5 Geographical source and type of malaria imported into the UK in 2011

	Africa	Asia	Other	Not given	Total
Plasmodium falciparum	989	10	3	147	1149
Plasmodium vivax	4	383	4	70	416
Other species/ mixed infections	97	3	0	14	112
Total	1090	351	7	229	1677

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Malaria

It is essential to consider and exclude or treat malaria, particularly as patients with falciparum malaria can deteriorate and develop severe complications within a few hours of presentation. In Britain, approximately 2,000 cases of malaria and 10 or so deaths are reported each year, a fatality rate of 1–2% in patients with falciparum malaria [65]. Higher mortality rates have been reported in other countries [66]. The number of tourists and expatriates who die overseas is not known. The majority of cases are imported by visitors and resident immigrants returning from a visit to their country of origin [65] and this pattern now predominates in other parts of Europe and North America. Table 15.5 summarises

the geographical origin of malaria reported in the UK in 2011; 16% of the patients were children, similar to earlier reports [63, 67]. An increasing proportion of cases in both adults and children in Britain and North America are due to falciparum malaria, when compared with previous decades. Most, but not all, falciparum malaria is imported from Africa and any patient with fever from Africa must be assumed to have falciparum malaria until proven otherwise. However, it cannot be assumed that patients from the Indian subcontinent always have benign vivax malaria, as the following case report demonstrates.

Case history

A 62-year-old Indian businessman based in Mumbai developed a nonspecific fever 2 days after travelling to Europe. This failed to respond to paracetamol and antibiotics prescribed by two different doctors. Fourteen days after leaving home he presented in Liverpool with cerebral malaria, renal failure and 22% falciparum parasitaemia. This fatal infection was acquired during a visit to a rural area in India without taking chemoprophylaxis.

This unfortunate history also emphasises that it is not just expatriates who fail to recognise that they are at risk of catching malaria when they travel to endemic zones. The majority of patients who present with imported malaria have failed to take adequate chemoprophylaxis. Poor outcome is usually associated with delays in presentation by the patient, failure of the attending physician to consider the diagnosis, and delays in arranging for diagnostic tests and treatment [66]. The travel population at greatest risk of dying from malaria includes the elderly, tourists (as opposed to travellers visiting friend and relatives), and those presenting in areas in which malaria is seldom seen [68].

The fever is of abrupt onset and is often mistaken for influenza, with headache, sweating, myalgia and in some cases paroxysms or rigors. Around 15% of malaria patients are afebrile at presentation or other symptoms may predominate, so that the diagnosis is not considered by the attending healthcare worker. In a recent audit in Liverpool, 31% of patients with falciparum malaria had diarrhoea as a prominent clinical feature, and in 16% of such cases malaria was not included in the admission differential diagnosis. Seventeen per cent had jaundice, which was sometimes ascribed to hepatitis rather than to malaria. Similar errors are commonly reported [66, 69] and emphasise the protean nature of malaria presentations (Table 15.6).

The timing of presentation of cases helps in the differential diagnosis of malaria. The majority of patients with falciparum malaria present within 6 weeks of leaving an endemic area, and over 90% present within 2 months. Patients taking chemoprophylaxis may have partial suppression of their parasitaemia, which both increases the clinical incubation period and hampers the laboratory diagnosis, as the lower degree of parasitaemia is more difficult to detect. Nevertheless, partial chemosuppression is better than none and probably reduces mortality in such patients.

Table 15.6 Common errors in diagnosis and management of malaria

Delayed presentation by patient
Failure of healthcare worker to take a travel history
Failure of healthcare worker to consider malaria in symptomatic patient
Belief that chemoprophylaxis prevents all malaria
Belief that malaria is unlikely to be present if patient does not remember being bitten by mosquitoes
Belief that absence of splenomegaly excludes malaria
Belief that absence of regular fever pattern excludes malaria
Failure to recognise non-specific clinical presentations of malaria
Failure to obtain good quality blood film diagnosis immediately (with species diagnosis)
Failure to obtain repeat films or use ancillary diagnostic tests if first films are negative
Failure to prescribe adequate and appropriate chemotherapy immediately
Failure to anticipate complications
Failure to treat complications
Failure to follow patient up after treatment

The non-falciparum malarias have a different spectrum of incubation and must always be considered in a patient who has been to an endemic region within the last 2 years. Approximately a third of patients with vivax malaria present within 2 months of arrival, and another third do not develop symptoms until 6–12 months after leaving a malarious area. Ovale malaria, usually from West Africa, presents with similar delays. Late presentations of vivax or ovale malaria should not be overlooked in a febrile patient who has been successfully treated for falciparum malaria several months earlier, as chemosuppression will have been discontinued and the treatment for falciparum malaria will not have treated the hypnozoites (quiescent liver stages) of the non-falciparum malarias. *Plasmodium malariae* has the potential to relapse for years but is only found in a small proportion of imported cases. It is rare for patients with recurring 'fevers' years after return from the tropics to have malaria; other diagnoses should be sought for such patients.

The physical findings in malaria are non-specific and malaria cannot be distinguished clinically from other

illnesses. Jaundice and diarrhoea have already been mentioned. Rashes suggest other illnesses, except in very rare cases of petechiae due to disseminated intravascular coagulopathy complicating falciparum malaria. The fever pattern of malaria, when present, is usually continuously elevated in falciparum infection. Parasite populations do not become synchronised (*see* Chapter 10) until at least the second week of clinical illness in the benign malarias, so that it is unusual to see the classical 48- or 72-hour pattern of fever produced by simultaneous lysis of erythrocytes and release of merozoites. Patients with malaria may have an enlarged liver, and splenomegaly is present in only a minority at presentation and has little positive or negative predictive diagnostic value.

The diagnosis of malaria can only be made by performing the appropriate laboratory tests.

Case history

A 55-year-old businessman consulted his general practitioner with fever 2 weeks after returning from a holiday in coastal Kenya. He took no prophylaxis as his daughter, an air stewardess, had told him that it would make him ill. The general practitioner sent a blood film to a local laboratory and did not receive their negative blood film report until 36 hours later. The patient continued to be unwell and was sent into hospital after a further 3 days, by which time he had 2% parasitaemia with falciparum malaria. Expert review of the original blood films later confirmed the presence of falciparum malaria.

In this case the general practitioner had done well to consider malaria, but there was a failure to obtain results within a few hours and the diagnosis was missed by an inexperienced laboratory. In all cases in which malaria is a possibility, results of good-quality blood tests must be obtained within half a working day at the most. In everyday practice, most family practitioners should refer such patients immediately to hospital for diagnosis, or to their regional specialist clinic if one is available.

Laboratory diagnosis of malaria

Malaria is conventionally diagnosed by examination of blood films for characteristic parasites within the erythrocytes. Thin blood films are routinely processed in most hospitals, but are not usually stained at the optimum pH for malaria diagnostics. Thin films are most valuable for confirming the species of parasite, especially in mixed infections, and for determining the degree of parasitaemia, but have low diagnostic sensitivity. In the tropics and in expert laboratories, examination of thick blood films is the preferred method because a larger volume of blood is examined in the film and sensitivity is improved. Few laboratories in western countries are proficient at this and numerous studies confirm that many diagnostic laboratories either cannot identify the species correctly (the usual problem) or fail to see parasites at all. In imported malaria cases, the first blood films are positive in more than 95% of cases examined by experts [66] but may genuinely be negative, especially if the patient is taking partially effective chemosuppression and parasitaemia is very scanty. Patients with negative films should have a second film examined 12 hours later, and possibly a third one 12 hours after that if clinical suspicion continues. The timing of taking the specimen in relation to fever is not clinically important.

Thus the conventional management approach to a patient with 'fever? malaria' is to admit to hospital for 24–48 hours for observation, syndromic management and blood films to rule out malaria, as well as other investigations. However, recent improvements in laboratory technology utilising rapid diagnostic tests (RDTS) are revolutionising this approach. The currently available RDTs detect one or more of the parasite antigens, histidine-rich protein 2 (HRP2], lactate dehydrogenase or aldose and are usually specific for *P. falciparum* infections, non-*P. falciparum* or mixed infections [70, 71]. RDTs are not as sensitive or specific as expert examination of thick and thin films, but are used in parallel, especially in settings where microscopy is not available. The sensitivities of commercially available RDTs are reported as approaching 100% but tests may remain falsely positive for several weeks after the infection has been treated due to persistence of parasite antigens in the bloodstream [72]. Most RDTs perform well for detection of *P. falciparum*, but have reduced sensitivity for *P. vivax* infection and low sensitivity for the three other species of malaria. There is considerable variability in the efficacy of RDTs between manufacturers, but this can be mitigated through the use of quality controlled tests by well trained personnel.

The dipstick RDT methods have the great advantage that they are less prone to observer error than film interpretation in less experienced laboratories, but they are not yet simple enough for travellers to use for self-diagnosis in remote situations [73]. The measurement of antibodies has no place in the routine diagnosis of patients with fever, but is used to make a retrospective diagnosis of recent malaria in previously nonimmune subjects, particularly in the context of detecting subclinical malaria infection in clinical trials or epidemiological studies. Polymerase chain reaction (PCR]-based tests are increasingly being used to monitor the quality of diagnostic laboratories [66, 74], for epidemiological investigations of unusual situations such as the nosocomial

Table 15.7 Laboratory diagnosis of malaria

Method	Uses	Comments
Thin blood film	Routine use in western laboratories Speciation; determination of parasitaemia	Insensitive
Thick blood film	Routine in tropics Approximate parasitaemia; speciation	Requires experience
Antimalarial antibodies	Retrospective diagnosis in returned travellers (e.g. trials)	Cross-reactions. Not useful for acute diagnosis
Quantitative buffy coat (QBC)	Diagnosis in inexperienced laboratories	Insensitive. No speciation Requires special equipment. Cost
Antigen detection based on histidine-rich protein 2 (HRP-2)	Current or recent falciparum malaria only Useful in inexperienced laboratories	Mainly for falciparum. Sensitivity equivalent to thick film. Stay positive for 1–2 weeks
Antigen detection based on lactate dehydrogenase (LDH)	Current malaria (species-specific) Useful in inexperienced laboratories May alert laboratory to mixed infections	Have largely replaced HRP-2-based tests Can also be used to monitor early success of therapy
Polymerase chain reaction (PCR)	Sensitive and species-specific; mainly for laboratory quality assurance and mixed infections	Not routinely available for diagnosis, but will soon do so; may be suitable for blood donation screening
Malaria pigment detection	Hypothetical method of automated counting	Speculative

transmission of malaria [74], or for detecting mixed infections. In some countries, PCR has already been introduced as an adjunct or alternative to microscopy, and the move for PCR to replace microscopy in well-resourced settings (where microscopists have less experience] will accelerate with the current development of more sensitive and suitable PCR techniques [75, 76].

Other approaches, such as the use of automated counters to detect malaria pigment in whole blood specimens, may produce new methods for diagnosis in the future [77]. Table 15.7 summarises the use of these tests.

Other causes of fever

The emphasis so far has been on malaria and its laboratory diagnosis. Other causes of fever can be determined by a combination of history, examination and laboratory investigations [54]. In practice, the most useful aid is a precise history of exposure or risk behaviour, together with recognition of the overall clinical pattern of presentation, as many features of febrile illness overlap. Risk activities such as those in Table 15.3 suggest the diagnosis and can be combined with the incubation periods (Table 15.2) and groups of physical signs in Tables 15.8–15.10, and routine laboratory tests may yield further clues.

The risk of viral haemorrhagic fevers (VHF] should be considered in all febrile travellers, particularly those for whom no diagnosis has been made and who become symptomatic within 21 days of leaving rural areas of sub-Saharan Africa. Approximately one case of Lassa fever is diagnosed every two years in travellers returning to the UK. Most patients acquired their infection in rural areas in Sierra Leone or Nigeria [8] and updated national British guidelines

Case history

A 23-year-old woman developed high fever, headache, back pain and a generalised blanching erythematous rash 3 days after returning from rural Thailand. The clinical diagnosis of dengue was confirmed by detection of antibodies 2 weeks later. This typical presentation of fever and rash with a short incubation period is highly suggestive of dengue fever, which is now widespread throughout Asia and South and Central America and the Caribbean, and is rapidly spreading through Africa [78]. Diagnosis is made using PCR in the first week of illness and by serological tests thereafter (these may cross-react with antibodies from prior yellow fever immunisation]. Recovery can be prolonged. Haemorrhagic complications are unusual in primary attacks in non-immune tourists (Chapter 6], but aspirin should not be used as an antipyretic in patients with possible dengue. Many other arboviral infections have similar presenting syndromes, the diagnosis being suggested by geographical exposure and confirmed by serology.

Table 15.8 Common syndrome/disease associations with imported fever

Sore throat	Cough	Abdominal pain	Arthralgia/myalgia	Diarrhoea
Bacterial pharyngitis	Amoebiasis (hepatic)	Amoebiasis (intestinal)	Arboviruses	Amoebiasis (intestinal)
Diphtheria	Anthrax	Anthrax	Dengue	Anthrax
Glandular fever	Bacterial pneumonia	Campylobacter	Yellow fever	Campylobacter
HIV seroconversion	Filarial fever	enteritis	Babesiosis	enteritis
Lyme disease	TPE	Legionnaires' disease	Bartonellosis	HIV seroconversion
Poliomyelitis	Histoplasmosis	Malaria	Brucellosis	Legionnaires' disease
Psittacosis	Legionnaires' disease	Measles	Erythema nodosum leprosum	Malaria
Tularaemia	Leishmaniasis (visceral)	Melioidosis	Hepatitis (viral)	Measles
Viral haemorrhagic fever (Lassa)	Loeffler syndrome	Plague	Histoplasmosis	Melioidosis
Non-specific viral upper	Malaria	Relapsing fevers	HIV seroconversion	Plague
respiratory tract infection	Measles	Salmonellosis	Legionnaires' disease	Relapsing fever
(URTI)	Melioidosis	Schistosomiasis (acute)	Leptospirosis	Salmonellosis
	Plague	Shigellosis	Lyme disease	Schistosomiasis (acute)
	Q fever	Typhoid in children	Malaria	Shigellosis
	Relapsing fever	Viral haemorrhagic	Plague	Typhoid in children
	Schistosomiasis (acute)	fevers	Poliomyelitis	Viral haemorrhagic
	Toxocariasis	Yersiniosis	Q fever	fevers
	Trichinosis		Relapsing fevers	Yersiniosis
	Tuberculosis		Secondary syphilis	
	Tularaemia		Toxoplasmosis	
	Typhoid and		Trichinosis	
	paratyphoid		Trypanosomiasis (African)	
	Typhus		Tularaemia	
	Viral haemorrhagic		Typhoid and paratyphoid	
	fevers		Typhus	
	Non-specific viral URTIs		Viral haemorrhagic fevers	

TPE = tropical pulmonary eosinophilia.

on the risk assessment, infection control and management of suspected VHF were published in 2012 [41]. If in doubt, clinicians are advised to avoid taking non-essential blood tests prior to consulting with infectious disease or microbiology services. Further details and current guidelines are available on the HPA and CDC websites.

Fever patterns are rarely useful at the bedside for differentiating the cause of illness, and the classical biphasic 'saddleback' fever of dengue is not often seen. Enteric fever (typhoid and paratyphoid) tends to cause a sustained fever but the 'classical' relative bradycardia is infrequent and is not diagnostic, as it may also be a feature of brucellosis and hepatitis.

Generalised rashes accompanying fever may be non-specific or suggest specific causes. A petechial rash is seen in meningococcal disease, a particular hazard for pilgrims to Mecca for the Hajj, and may accompany any septicaemic illness. Maculopapular rashes are seen with most rickettsial illnesses, a further clue to which is the presence of an eschar at the site of tick or mite bites in tick typhus or scrub typhus, respectively.

Focal solitary skin lesions with fever raise the possibility of African trypanosomiasis, in which the initial tsetse fly bite

Case history

A middle-aged couple were admitted to hospital on return from a 2-week safari holiday in South Africa with identical symptoms of headache, malaise, fever, dry cough and tender maculopapular rash on their legs. Single eschars, consisting of a necrotic black central skin lesion surrounded by erythema, were found in both patients. The lesion in the woman was under her bra strap, and her husband's was located under the elastic of his underwear. Both patients responded promptly to doxycycline therapy, which was given as soon as the clinical diagnosis of African tick typhus was made. Serology later became positive for infection with *Rickettsia africae*. This is a typical presentation of tick typhus. The tick bite is not usually remembered by the patient, who may also have overlooked the eschar, which is sometimes located in the scalp, in which case regional lymphadenopathy may provide a clue to its presence. Rashes are less common in African tick typhus than in Mediterranean tick typhus and murine typhus.

Table 15.9 Neurological syndrome/disease associations with imported fever

Fits	Meningitis/encephalitis
Arboviruses	Angiostrongyloidiasis
Japanese encephalitis	Anthrax
Bacterial meningitis	Arboviruses
Histoplasmosis	Chikungunya
Malaria	Dengue fever
Rabies	Japanese encephalitis
Shigellosis (children)	West Nile fever
Tetanus	Yellow fever
Tuberculosis	Bacterial meningitis
meningitis	Histoplasmosis
tuberculomata	HIV seroconversion
	Legionnaires' disease
	Leptospirosis
	Lyme disease
	Malaria
	Poliomyelitis
	Rabies
	Relapsing fevers
	Secondary syphilis
	Trypanosomiasis (African)
	Tuberculosis
	Typhoid and paratyphoid
	Typhus

at the site of the subsequent chancre is usually vividly recalled by the patient. Similar chancres (chagomas) may be seen at the site of bites by reduviid bugs that transmit *Trypanosoma cruzii* in South America. Lyme disease may present with focal or migrating erythema at the site of the initial tick bite, which is not always recalled.

Non-specific rashes accompany fever due to other infections, including rarities such as the viral haemorrhagic fevers (facial oedema is a clue in early Lassa fever) and African trypanosomiasis. The classical rose spots of typhoid are only seen transiently in pale-skinned patients in the second week of illness, and consist of blanching macules 2–3 mm in diameter. These should not be mistaken for the rash of secondary syphilis or disseminated gonococcaemia.

Lymphadenopathy is typically a feature of the 'glandular fever' group of infections, seen commonly in young adults, including infectious mononucleosis, cytomegalovirus and toxoplasmosis, and is also found in dengue fever, brucellosis and a wide variety of other infections (Table 15.10). Malaria does not cause lymphadenopathy. Acute HIV seroconversion illness is often accompanied by lymphadenopathy (which is also common in chronic HIV infection) and this should always be part of the differential diagnosis.

Case history

A 32-year-old man was referred by his general practitioner with possible typhoid because of fever, headache, diarrhoea and a non-specific pink maculopapular rash on his torso. He also had lymphadenopathy. He had returned 4 weeks previously from a visit to Thailand, where he had unprotected sex. Initial HIV antibody tests were negative, although a blood test for HIV antigen was positive. His antibody tests became positive 6 weeks later.

All of the above features are common in HIV seroconversion illness, during which conventional HIV antibody detection tests are usually negative. The importance of the exposure history is self-evident.

Focal lymphadenopathy is usually associated with regional sepsis, most commonly infected skin wounds and arthropod bites, but rarities such as plague (exquisitely tender unilateral nodes or buboes) should also be considered, as well as more common illnesses such as tuberculosis.

Jaundice is a feature of many illnesses, including malaria, viral hepatitis, leptospirosis, the glandular fever group and arbovirus infections such as yellow fever.

Case history

A 33-year-old man developed headache, fever, myalgia and jaundice 10 days after white-water rafting in Thailand. He had meningism, jaundice, tender muscles, splenomegaly and mild renal failure. He had been immunised against hepatitis A and B before travel and serological tests subsequently confirmed infection with leptospirosis.

Leptospirosis is found worldwide and the history of exposure to fresh water is typical, particularly in Asia, where large epidemics affect the local population each year. In the absence of other focal features and specific exposure history, viral hepatitis should be considered as the cause of jaundice. Hepatitis A is still a hazard for non-immunised travellers; hepatitis B and C are both transmitted by unsterile injections and infusions; and hepatitis B is a risk after unprotected sexual exposure. Water-borne hepatitis E is endemic and also causes sporadic epidemics in the Indian subcontinent, in much of adjacent Asia and in Mexico, and is probably underrecognised in most other parts of the tropics. It should be suspected in jaundiced travellers to Asia who are immune to hepatitis A and have not been immersed in fresh water. Serological tests are essential to differentiate the causes of viral hepatitis, which are indistinguishable clinically (*see* Chapter 7).

Table 15.10 Possible association of physical signs with imported infections

Lymphadenopathy	Hepatomegaly	Splenomegaly	Jaundice
Arboviruses (dengue)	Amoebiasis (hepatic)	Babesiosis	Cytomegalovirus
Bartonellosis	Babesiosis	Bartonellosis	Fascioliasis
Brucellosis	Bartonellosis	Brucellosis	Hepatitis (viral)
Cytomegalovirus	Brucelolosis	Cytomegalovirus	Leptospirosis
Diphtheria	Cytomegalovirus	Erythema nodosum leprosum	Malaria
Erythema nodosum leprosum	Dengue	Filarial fever (TPE)	Relapsing fevers
Filarial fever	Fascioliasis	Hepatitis (viral)	Toxoplasmosis
Histoplasmosis	Hepatitis (viral)	Histoplasmosis	Trypanosomiasis
HIV seroconversion	Histoplasmosis	HIV	African, acute
Infectious mononucleosis	HIV seroconversion	Leishmaniasis (visceral)	Typhoid and paratyphoid
Leishmaniasis (visceral)	Legionnaires' disease	Lyme disease	Typhus
Lyme disease	Leishmaniasis (visceral)	Malaria	Yellow fever
Plague	Lyme disease	Melioidosis	
Psittacosis	Malaria	Psittacosis	
Q fever	Q fever	Q fever	
Schistosomiasis (acute)	Relapsing fevers	Relapsing fevers	
Secondary syphilis	Schistosomiasis (acute)	Salmonellosis	
Toxoplasmosis	Toxocariasis	Schistosomiasis (acute)	
Trichinosis	Trypanosomiasis	Toxoplasmosis	
Trypanosomiasis	African, acute	Trichinosis	
African, acute	America, acute	Trypanosomiasis	
American, acute	Tuberculosis	African, acute	
Tuberculosis	Typhus	American, acute	
Tularaemia		Tuberculosis	
Typhus		Tularaemia	
		Typhoid and paratyphoid	
		Typhus	

TPE = tropical pulmonary eosinophilia.

After malaria, respiratory infections are the most common causes of imported fever, with or without localising signs. Most are due to cosmopolitan infections, such as influenza and other respiratory viruses, or community-acquired pneumonia. Influenza is the most common vaccine-preventable travel-related infection. Rare but important causes of pharyngitis include diphtheria (look for membrane) and Lassa fever (exposure in rural West Africa). It is impossible to distinguish the different causes of community-acquired pneumonia at the bedside, and the usual conventional diagnostic tests should be employed, including convalescent serological tests several weeks after the onset of illness.

Of particular importance to travellers is the increasing prevalence of multi-drug resistant *Streptococcus pneumoniae* in many countries, including most of the Far East, Papua New Guinea, South Africa and Spain, so that therapy with penicillin is inappropriate for travellers from these areas. Legionella infection imported to the UK is typically associated with travel to Mediterranean resorts and with cruises or contaminated air conditioners or showers in hotels. Surveillance suggests that approximately a quarter of legionella infections are associated with recent travel [80, 81]. The older patient who smokes and drinks alcohol to excess is most likely to develop severe disease; he or she is also most likely to have delayed antibody seroconversion, so that serological tests may not become positive until 6–8 weeks after onset of illness. Other clues to atypical pneumonia pathogens include contact with animals for Q fever (splenomegaly, thrombocytopenia) and tularaemia (lymphadenopathy), and with psittacine birds (psittacosis).

Hantavirus infections transmitted by rodent contact, such as *sin nombre* virus, are increasingly being recognised as causes of severe atypical pneumonia in visitors to rural areas of the USA or South America [8, 82].

A non-productive cough is found in typhoid fever and brucellosis, often without radiographic abnormality. Fever with wheezy cough or asthmatic presentation is a feature of filarial tropical pulmonary eosinophilia (TPE) and of the

migratory phase of immature stages of many nematode and trematode infections, including hookworms, roundworms and schistosomes. In these situations, eosinophilia will suggest the diagnosis (see Eosinophilia, below).

Haemoptysis suggests tuberculosis (or tumour), but travellers who have eaten raw crustacea in the Far East, West Africa or South America may have paragonimiasis, which can be mistaken radiologically for tuberculosis and is diagnosed by looking for characteristic ova in sputum.

Imported infections may produce a variety of neurological or psychiatric syndromes. In addition to the usual bacterial pathogens causing meningitis, infections such as brucellosis, leptospirosis, rickettsial illness and arboviruses frequently have a meningoencephalitic element. Drowsiness, meningism, focal neurological signs or progression to coma are all features of malaria, which must always be excluded, as must trypanosomiasis in travellers who have visited Africa. Transient psychological problems are common in travellers and are often associated with alcohol or drug misuse or rapid translocation between cultures. Rabies should be considered in patients who behave abnormally and may have had exposure to animals in the tropics, even if they do not remember the bite or lick.

Case history

A 47-year-old Indian seaman was admitted with fever and rigors for 4 days, accompanied by headache and mild diarrhoea. He had a high fever and developed right shoulder-tip pain the next day, when he was observed to have a tender, enlarged liver with a right basal pleural effusion. His blood count showed neutrophilia, and ultrasound confirmed the presence of a large abscess in the right lobe of the liver. Liver function tests were normal and amoebic serology was strongly positive. He responded rapidly to metronidazole.

This typical history emphasises the need to re-examine patients carefully and to consider amoebic liver abscess in occult fever. The presence or absence of diarrhoea or of trophozoites or cysts of *Entamoeba histolytica* in the faeces is of no diagnostic value, but neutrophilia is supportive and serology is usually positive at presentation.

In the absence of the above syndromes, physical examination should exclude other organ-based infections, including mundane sinusitis and ear infections. Focal signs may be diagnostic.

Diarrhoeal illness is common while travelling [11, 13, 83] but is self-limiting in the majority of cases (*see* Chapter 13). The usual bacterial and viral causes are implicated and enterotoxigenic *Escherichia coli* is over-represented in travellers with diarrhoea on their return home [84]. Cholera is rarely imported by travellers, partly because of the lack of risk to travellers while overseas and mainly because the incubation period is so short that most patients need medical treatment before repatriation. Diarrhoea is a feature of many of the febrile infections already described and is more likely to cause fever in children than in adults. Children with enteric fever are also more likely to have diarrhoea than adults. Diarrhoea with blood, fever and systemic illness is usually due to *Campylobacter*, *Shigella* or *Salmonella* spp, but the recent traveller with bloody diarrhoea (dysentery) and without much general illness may have amoebiasis. This is confirmed by examination of unpreserved faeces (the 'hot stool') or rectal scrapings within 20–30 minutes for active trophozoites of *Entamoeba histolytica* containing ingested erythrocytes. If these infections are excluded, the patient will need a further work-up, including lower bowel endoscopy, to exclude underlying gastrointestinal disease or chronic tropical conditions such as schistosomiasis. Watery diarrhoea caused by Cyclospora infections is also diagnosed by faecal microscopy, and is suggested by a history of travel to known endemic areas such as Nepal or Peru. Co-trimoxazole is effective treatment, with ciprofloxacin as an alternative.

In about 3% of cases, travel-related diarrhoea lasts for more than 14 days [11, 83]. Patients need a full work-up to exclude underlying immunosuppression, especially HIV, and adequate faecal tests for bacterial and parasitic (protozoan) parasites. *Giardia lamblia* is the most common culprit, typically causing explosive steatorrhoic diarrhoea in the mornings and often associated with 'eggy burps'. Untreated, the patient can develop significant malabsorption. Parasitological diagnosis may be difficult and many physicians opt for empirical therapy with agents such as tinidazole or metronidazole. Failure to respond to therapy may represent drug resistance [12] but is more likely to be due to failure to take the medication (ask the patient), or to transient lactase deficiency (exclude all lactose-containing food and drink for 1 week) or to reinfection by other family members. If all the above have been excluded, second-line drugs such as mepacrine or paromomycin may be needed.

Apart from the exclusion of underlying gastrointestinal disease, schistosomiasis or post-infectious irritable bowel syndrome, tropical sprue must be considered. The aetiology of tropical sprue is unknown and it causes persistent small bowel diarrhoea and malabsorption and requires a full expert diagnostic work-up. Treatment with tetracyclines, folic acid and vitamin B_{12} is effective [85].

Investigation of fever

Baseline investigations include a full blood count, including differential white count and platelet count, serum

electrolytes and liver function tests, blood cultures and malaria films. Urinalysis and cultures of urine and stool should be sent and a sample of serum stored for possible serological testing. The need for chest X-ray and other focal imaging, such as ultrasound of the liver, may be suggested by clinical findings. As indicated in the cases already presented, the potential list of serological tests and other investigations can be extensive but practitioners should resist the temptation to order everything just because the patient has travelled to an exotic country. Special examinations include microscopy of cerebrospinal fluid (CSF) for trypanosomiasis, bone marrow culture for partially treated typhoid or brucellosis, or bone marrow for microscopical examination for visceral leishmaniasis [54].

The initial emphasis should be on excluding malaria and infections of chest, urine or gastrointestinal tract before focusing on the most likely exotic diagnosis if these investigations prove negative. Convalescent serology taken at least 2 weeks later is often needed to make a retrospective diagnosis if this is thought to be important after the patient has recovered.

The small risk of transmission of infection to healthcare workers should always be kept in mind and appropriate infection control precautions should be taken. For patients with suspected diphtheria or with a possible viral haemorrhagic fever, more stringent isolation is needed and immediate advice should be obtained from public health specialists as well as from infectious disease experts [41, 42].

Blood films for malaria can also be used to exclude borreliosis, filariasis, babesiosis and African trypanosomiasis. Neutropenia is an inconsistent finding in malaria, viral infections and typhoid, and must be interpreted with caution, as the normal neutrophil and platelet counts are lower in patients of African ethnic origin than Caucasians [86]. Neutrophilia usually suggests a pyogenic bacterial infection but is also seen in malaria, and eosinophilia suggests a helminth infection or atopy. Thrombocytopenia is present in the majority of malaria infections and may alert the microscopist to the presence of parasitaemia, but it is also found with dengue, brucellosis, enteric fever, rickettsiosis, HIV and many viral infections [87]. A combination of thrombocytopenia ($<150 \times 10^9$/l) and raised bilirubin (>18 μmol/l) was found to have a positive predictive value of 95% and specificity of 98%, but a low sensitivity in diagnosing malaria in one study in London [57]. However, this combination was only found in 36 of the 82 patients with malaria, limiting the diagnostic usefulness to a small proportion of patients. Hypoglycaemia may also suggest malaria or African trypanosomiasis. Liver function abnormalities are rarely of specific diagnostic value but are helpful in assessing disease severity.

Treatment

A sequential approach to the diagnosis and treatment of the patient with imported fever is summarised in Figure 15.1. For details of specific treatment of most infections, the relevant chapters in this book should be consulted. The pharmacological management of malaria and its complications are described in full in Chapter 10 and in national malaria treatment guidelines [88, 89].

A few principles guide malaria treatment, once the diagnosis has been confirmed. Treatment should cover falciparum malaria unless there is a confident expert laboratory diagnosis of another *Plasmodium* species. Patients with falciparum malaria should usually be treated as inpatients for at least the first 24–48 hours in western settings, unless they are recent immigrants (with partial immunity) with very mild infections. Therapy is usually initiated via the parenteral route in severe or complicated falciparum malaria, one of the definitions of which includes hyperparasitaemia, and the level of parasitaemia must always be measured. Although the World Health Organization (WHO) defines hyperparasitaemia as a parasite rate > 5%, the majority of tropical specialists use a pragmatic cut-off level of 2% parasitaemia to indicate increased clinical risk in non-immune travellers with imported malaria. Children and pregnant women are particularly likely to experience hypoglycaemia as a complication of falciparum malaria. This may be exacerbated by quinine therapy, and blood glucose levels should be monitored before and during treatment.

Intravenous quinine was previously the drug of choice for the treatment of severe *P. falciparum* malaria and is still used when artesunate is not immediately available and in non-severe cases who cannot tolerate oral medication. Artesunate is increasingly recommended for the treatment of severe malaria due to its survival advantage compared to intravenous quinine [90]. There also increasing concern of the spread of quinine resistance from south-east Asia.

Artesunate is given as an intravenous infusion over 4hrs, with a loading dose followed by 8hrly dosing. If intravenous infusion is not possible, it may be administered by the intramuscular route or rectally. Cardiac monitoring is required, particularly in older patients or those with pre-existing cardiac disease due to the risk of arrthymia. Unfortunately, artemisinin-resistant malaria has already been demonstrated and is starting to emerge on the Thai-Cambodian border [91]. There is no added benefit to be gained by giving quinine and artesunate together.

Parasite rates should be estimated at least daily until negative and the patient must be followed up early after discharge to detect recrudescence due to resistance or inadequate treatment. Concurrent infections, particularly bacteraemia [92], should be considered in severe malaria, with a low threshold

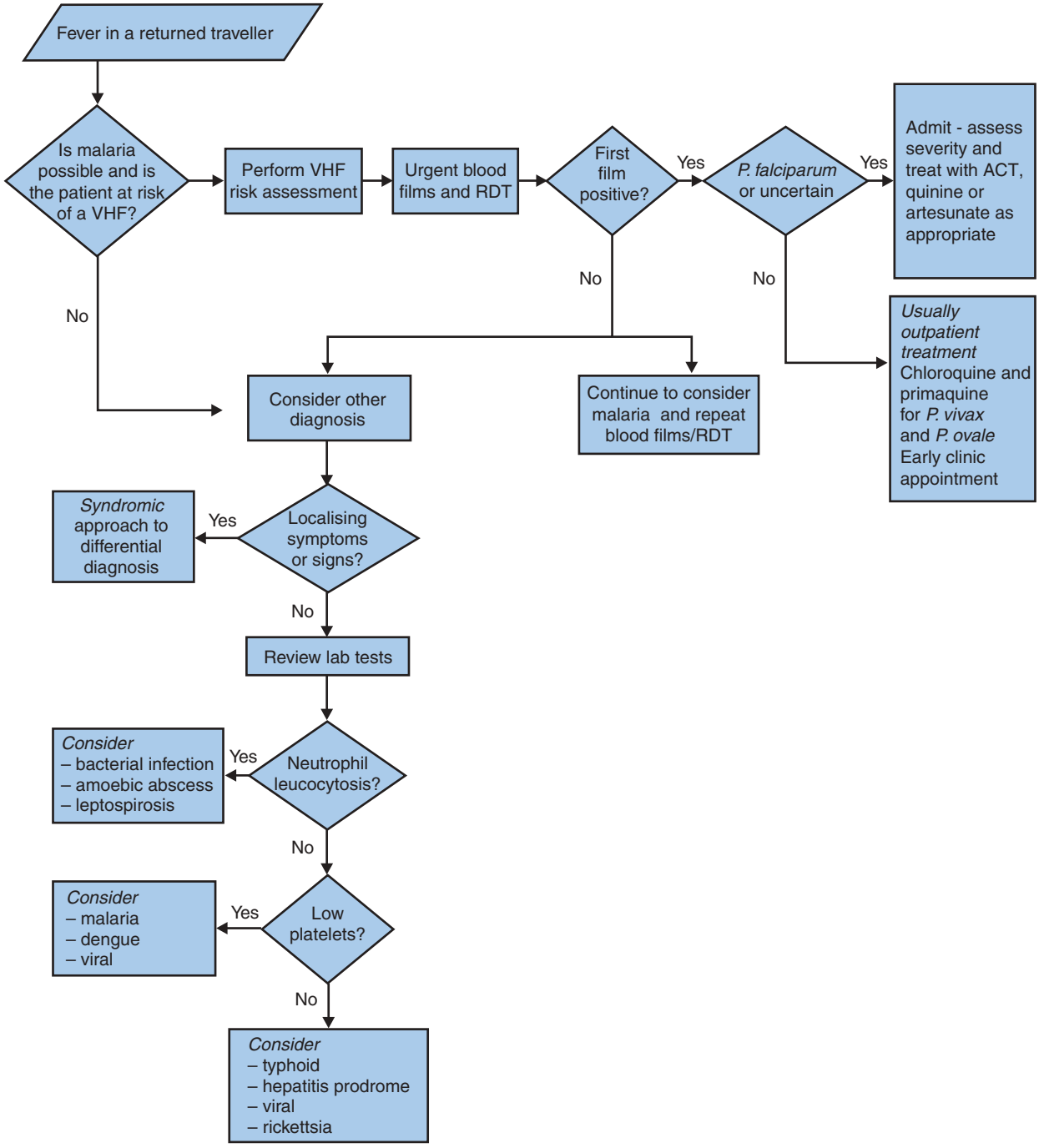

Figure 15.1 Algorithm for diagnosis of fever in the returned traveller. (Modified from [98], and reproduced with permission)

for introducing broad-spectrum antibiotics pending the results of blood cultures. Careful attention should be paid to fluid balance and monitoring renal, hepatic, neurological and respiratory function, and ill patients should be managed in a high dependency or intensive care setting. There is a theoretical advantage in removing parasitized red blood cells in patients with extremely high parasite counts by exchange transfusion, but there is no evidence to support the use of this [93]. With the increasing utilisation of artesunate therapy in severe cases, and its rapid parasite clearance, any

potential benefit is limited and as such it is not recommended. If it is being considered, individual cases should be discussed with malaria experts at either the Liverpool or London School of Tropical Medicine.

In less severe cases of falciparum malaria, artemisinin combination therapy (ACT] is recommended as first-line treatment by the World Health Organisation, and is being increasingly utilised in Western settings. ACT is attractive as it has a shorter treatment duration (3 vs. 7 days], more rapid action and better tolerability than quinine [94]. Patients with non-falciparum malaria can be managed, often as outpatients, with chloroquine, which is followed by primaquine to eradicate the hypnozoite stages of vivax and ovale malaria to prevent late relapse (not required for *P. malariae* or *P. knowlesi*). Resistance to both agents is present in the Pacific 'Chesson' strain of *P. vivax* and is increasingly seen in vivax malaria imported from other areas, including India [95]. However, treatment should be started with chloroquine even if resistant vivax is suspected, and can be switched later if there is no response. Life-threatening complications of vivax malaria are being reported more often in returned travellers [96]. These include acute respiratory distress syndrome, renal failure, severe hepatitis, coma and splenic rupture [97]. The pathogenesis is poorly understood but is not thought to relate to sequestration of parasites.

Skin disease

The most common dermatological problems in travellers are caused by overexposure to sun and insect bites [99, 100]. A variety of hypersensitivity reactions can follow arthropod bites and these, together with complicating staphylococcal and streptococcal infections, are common reasons for travellers to consult their family doctor after return. Suntans will also make dermatophyte infections such as pityriasis versicolor more obvious to the patient.

Cutaneous larva migrans is frequently seen in the clinic.

Case history

A young British couple had been for their honeymoon in the Caribbean. One week after their return, both developed multiple red serpiginous raised lesions on their legs and abdomen. Both had been lying on the sand to sunbathe. The rash persisted for a week until treatment with albendazole.

The tracks are caused by animal hookworms that invade skin in contact with sand or soil contaminated by cat or dog faeces. This common problem can be avoided by wearing shoes and not lying directly on the sand (use a sun lounger) or by choosing the part of the beach that is regularly cleaned by tidal action [101, 102]. Treatment of single lesions can be performed by applying a topical paste of tiabendazole but this is rarely available and a short course of albendazole or ivermectin is very effective.

Other invasive parasitic skin diseases are described in the section on eosinophilia, below. The most frequent delayed skin lesion seen in travellers is cutaneous leishmaniasis, particularly in people who have travelled in rural or forested areas of South and Central America or in the Indian subcontinent, although the cutaneous leishmaniases have a widespread geographical distribution (*see* Chapter 9). The rash typically starts as a papule that enlarges and ulcerates with indurated edges. The lesion slowly expands over weeks and is usually relatively painless unless there is bacterial superinfection. Lesions are usually on the face or peripheral parts of the limbs that have been exposed to sandfly bites, and may be single or multiple. There is often local lymphadenopathy and careful examination may reveal smaller nodules proximal to the main lesion. Most patients present within 6 months of exposure. There is no systemic upset and patients are often treated unsuccessfully for suspected staphylococcal infection before referral to a specialist clinic for investigation. Diagnosis is made by aspirating material from the active edge of the lesion or by making an impression smear from the lesion and staining with Giemsa for amastigotes. Special culture media are needed to grow the organism and species-specific PCR is a quicker and more sensitive method of confirming the diagnosis [103]. Infections with *Leishmania tropica* from India and the Middle East do not usually need specific treatment, but *L. braziliense* lesions should be treated by specialists with parenteral antimonial agents because of the small risk of mucocutaneous dissemination [104, 105]. *L. braziliense* lesions cannot be distinguished clinically from those caused by *L. mexicana* and other Central and South American species.

Myiasis is a frequent problem in travellers to Africa. The tumbu fly, *Cordylobia anthropophaga*, lays its eggs on clothes and the larvae from these directly invade the skin, producing lesions resembling a staphylococcal boil. At the centre of these the tip of the larva can be seen to wriggle. Treatment is by suffocating the larva with topical petroleum jelly, then careful removal with forceps as it extrudes itself to obtain air. Travellers to South and Central America may acquire more invasive cutaneous myiasis due to larvae of *Cochliomyia hominivorax* or *Dermatobia hominis*. These larvae have lateral spines that make removal more difficult, often requiring minor surgery under local or even general anaesthetic. The 'jiggers flea', *Tunga penetrans*, frequently infects the feet of people who walk barefoot in the tropics. The female flea,

full of eggs, grows to cause a nodule, from which it can be carefully shelled out with a toothpick or needle. Care should be taken not to rupture the flea, which could lead to local bacterial infection.

Eosinophilia

A raised eosin count usually suggests a helminth infection in returned travellers. Although the traditional definition of eosinophilia is an absolute count $> 0.44 \times 10^9$/l, many clinicians use a cut-off level of $> 0.5 \times 10^9$/l in working practice [106, 107]. This level of eosinophilia is used for travellers returning from the tropics, but no normal ranges have been published for those who live in the tropics long term.

Up to 10% of the travelling population have atopic conditions, such as eczema or asthma, which cause a raised eosinophil count, and some medications such as non-steroidal anti-inflammatory agents also cause a raised count. A wide variety of nematode and trematode infections produce eosinophilia, particularly during the migratory phases of larvae through the body (Table 15.11). Some of these, such as hookworms, roundworms and *Strongyloides* spp are universally distributed in the tropics, while other parasitic infections will be suggested by the specific travel history of the patient and by the symptoms and physical findings.

Table 15.11 Selected parasitic infections and eosinophilia in travellers

Parasite/disease	Clinical clues
Nematodes	
Ascaris lumbricoides	Visible worms in faeces; Loeffler
Hookworms	Anaemia; Loeffler
Strongyloides spp	Diarrhoea; larva currens rash
Trichuris trichiura	Diarrhoea (bloody)
Loa loa	Travel history; visible worm in eye; Calabar swelling
Mansonella perstans	Travel history
Onchocerca volvulus	Travel history; eye symptoms; rash; nodules
Wuchereria bancrofti *Brugia malayi*	Travel history; sometimes tropical pulmonary eosinophilia; rarely chyluria, elephantiasis, etc.
Nonhuman hookworms	Rash of cutaneous larva migrans
Trematodes	
Schistosoma spp	Travel history and freshwater exposure; Katayama fever; haematuria or blood in faeces
Fasciola hepatica	Travel history; tender enlarged liver
Clonorchis spp *Opisthorcis* spp	Travel history; cholangitis-like presentation
Paragonimus spp	Travel history and food history; haemoptysis

Asymptomatic schistosomiasis is a common imported cause of eosinophilia: a history of immersion in fresh water in Africa, the Middle East or in much of the Far East or South America should always be sought. Only a minority of patients recall having 'swimmer's itch' 24–48 hours after bathing in infected water, caused by the initial penetration of skin by the schistosomule. As in the case report illustrated, of the 19-year-old student, acute schistosomiasis may cause symptoms in non-immune travellers 3–8 weeks later as the larvae begin to mature and to excrete eggs, which elicit an eosinophilic response. Patients experience fever, transient urticarial rashes, headache, a dry cough and malaise (Katayama fever) [108]. Hepatosplenomegaly is occasionally found and transitory non-specific infiltrates may be seen on chest X-ray [109]. High levels of eosinophilia ($>1 \times 10^9$/l) are common at this stage but specific diagnostic tests are usually negative. The condition settles and the patient may then remain asymptomatic or subsequently develop haematuria, alteration in colour and/or consistency of semen [110], or blood in the faeces. By this stage, serological tests and microscopy of terminal urine specimens, filtered urine collections (*Schistosoma haematobium*) and stool or rectal snips (*S. japonicum*, *S. mansoni*) should be positive [111]. Treatment with praziquantel during the acute state has no effect on migrating schistosomules and we repeat the treatment 3 months later. The role of a short course of steroids in Katayama fever is unproven but they are often used for patients who are ill enough to merit treatment in hospital [112]. Haematuria requires further investigation and follow-up for possible complications. Patients with schistosomiasis can be treated as outpatients and should be followed up to confirm parasitological cure. This is important as ectopic egg deposition may cause crippling transverse myelitis later on if the patient is not cured [113]. The enzyme-linked immunosorbent assay (ELISA) titre often rises initially and can take several years to become negative. This reduces its usefulness for diagnosis of new infection after repeated exposures during subsequent travels.

Schistosomiasis is the most common cause of eosinophilia in travellers from Africa seen in our clinic or in London. The next most common systemic cause is filarial infections. Onchocerciasis is still a major problem in West Africa, the Yemen and in Central and South America (*see* Chapter 9). Patients are often asymptomatic or present years after exposure with itchy skin. Occasionally nodules containing adult worms can be found, and fundoscopy should always be performed to detect choroidoretinitis, which leads to blindness. Diagnosis is usually confirmed by examining skin snips for motile larvae. Treatment with diethylcarbamazine (DEC) is

invariably followed by an allergic reaction (the Mazzotti reaction), which can be severe enough to cause hypotensive collapse in heavily infected patients. It can be used to confirm the diagnosis in skin snip-negative patients by giving a small dose of DEC. This reaction is much less common following the current treatment of choice, which is ivermectin, but expatriates should still be treated under hospital supervision.

Loiasis infection is relatively common in people who have visited West Africa, some of whom may complain of transient oedematous swellings of the limbs (Calabar swelling). Patients occasionally notice the larvae migrating under the conjunctiva of the eye, where they are readily visible to the healthcare worker. Patients with *L. loa* should always be investigated with skin snips to exclude coexistent onchocerciasis, especially if they are to be treated with DEC, when pretreatment with steroids is used by some [114]. Ivermectin or possibly albendazole are now the treatments of choice and heavy filarial loads may need to be reduced by plasmapharesis prior to chemotherapy.

Other blood and lymphatic filariases have a more widespread distribution in the tropics and are common causes of eosinophilia in Asia and the Pacific region, as well as in Africa and South and Central America. Infections are usually asymptomatic but the early phase of infection is characterised by wheezing, dyspnoea, cough, fever and fatigue, with widespread shadowing on the chest X-ray (tropical pulmonary eosinophilia). Eosinophil levels are very high ($>3 \times 10^9$/l) but microfilariae are not found in the blood. Serological tests (ELISA) for filariasis are positive. Symptoms may require relief with a short course of steroids. This condition is less commonly seen in travellers after their return, when filariasis is usually asymptomatic. Emergence of the microfilariae of *Wuchereria bancrofti* into the bloodstream is nocturnal and they are most easily found in blood taken at midnight. Daytime blood samples are positive if the patient is given a single dose of DEC 1 hour beforehand. Other filarial infections do not usually have nocturnal periodicity and can routinely be detected in daytime blood films. Treatment is with DEC, ivermectin or albendazole. The use of doxycycline against the symbiotic *Wolbachia* species within most filariae has been promising in reducing embryogenesis of microfilariae for up to 18 months after treatment [115]. It also has modest activity against the adult worm and individualized treatment with doxycycline can be considered. Rifampicin or azithromycin might also be used but have yet to show superiority to doxycycline [116].

After excluding schistosomiasis and filarial infections, the most common imported causes of eosinophilia are intestinal nematode infections such as hookworm infection, trichuriasis and strongyloidiasis. *Trichuris trichuria* is often asymptomatic but heavy infections can cause bloody diarrhoea and even rectal prolapse in young children. Patients with hookworm may have abdominal pain but anaemia is only caused by heavy infections, especially in malnourished children.

Tapeworm infections of the gut are often associated with moderate eosinophilia but are not common in returned travellers. They are diagnosed by finding proglottids in stool which are visible to the naked eye. Treatment is with praziquantel. Hydatid cysts rarely cause a raised eosinophil count unless they have ruptured or leaked. Ascaris and hookworms can also cause transient parasitic pneumonitis (Loeffler syndrome) during the pulmonary larval migration phase. This is less severe than tropical pulmonary eosinophilia, from which it can be distinguished by negative filarial ELISA tests, and blood films for microfilariae are also negative. Eosinophilia can also accompany cutaneous larva migrans caused by non-human hookworm larvae or the transient rash (ground itch) that is occasionally seen in non-immune travellers following skin penetration by larvae of human hookworms. These rashes should be distinguished from the 'larva currens' rash of *Strongyloides stercoralis* infection, which can persist for decades by autoreinfection.

Intestinal nematodes can usually be identified by stool microscopy, but this is often negative in *Strongyloides* infections, for which special culture methods are needed, together with specific ELISA tests on serum. Strongyloidiasis should be excluded in patients who are about to undergo chemosuppressive therapy, and who have travelled or were born in the tropics or subtropics, because of the risk of fatal hyperinfection syndrome.

Case history

A 45-year-old Nigerian man presented to our clinic 10 years after leaving West Africa with chronic, non-bloody diarrhoea and weight loss. On direct questioning he admitted to occasional rashes that consisted of a linear urticarial track moving rapidly across his abdomen for 24–48 hours. He had high eosinophilia, a positive serum ELISA for *Strongyloides*, and positive charcoal culture of faeces for the characteristic larvae of *S. stercoralis*. His symptoms resolved after treatment with ivermectin.

Patients in whom the above infections have been excluded as causes of eosinophilia may harbour fluke infections from ingestion of raw foods and a careful history should be sought about dietary habits while travelling. Consumption of contaminated salads or cress is associated with fascioliasis, particularly in the Middle East. Patients experience painful hepatomegaly and fever during the migratory phase, with alarming findings on ultrasound of holes in the liver resembling peliosis hepatis. Serological tests may be helpful, as the

characteristic ova may be difficult to find in stools. Patients who have eaten raw fish, crabs or other freshwater crustacea in the Far East may acquire clonorchiasis or paragonimiasis, producing cholangitis and haemoptysis, respectively. Ingestion of frogs in the Far East can transmit gnathostomiasis, characterised by solitary swellings, often on the face, which persist for days to weeks. Ingestion of slugs or snails (usually inadvertently in salads) in much of the Pacific region can result in eosinophilic meningitis. This presents acutely with fluctuating focal neurological signs and meningitis, with eosinophils in peripheral blood and CSF. Eosinophils are occasionally seen in the CSF of patients with neurocysticercosis, which may cause epilepsy years after acquiring *Taenia solium* following ingestion of pork. Subcutaneous nodules may be present and calcified cysts can be visualised in plain X-ray films of the thighs. Computed tomography or magnetic resonance imaging of the head confirms the diagnosis. Trichinosis and visceral larva migrans (toxocariasis) are cosmopolitan infections that should be considered in the differential diagnosis of eosinophilia but are not specifically associated with travel [117]. Other causes of myositis and eosinophilia include sarcocystis infection, recently reported in travellers returning from Malaysia [118].

The investigation of eosinophilia may be a protracted process. A useful scheme is summarised in Figure 15.2: more complex protocols have been devised for travellers from different geographical regions [106, 107]. Simple investigations, including examination of at least two faecal specimens for ova and larvae, and blood for microfilariae, should precede more focused serological and parasitological tests of skin snips, sputum and duodenal samples. The exposure history or clinical picture may also suggest the need for specific tests such as imaging of the liver. If these fail to provide a diagnosis, treatment with a broad-spectrum agent, such as albendazole, with follow-up to establish resolution of eosinophilia is usually adequate and had been shown to be cost effective [119]. Alternatively, the patient can be observed for 2–3 months and a repeat stool examination performed to detect parasites that have completed their development and are now excreting ova. It should be remembered that the absence of eosinophilia does not exclude helminth and cestode infections, which should be investigated as in Figure 15.2 if there is clinical suspicion for other reasons.

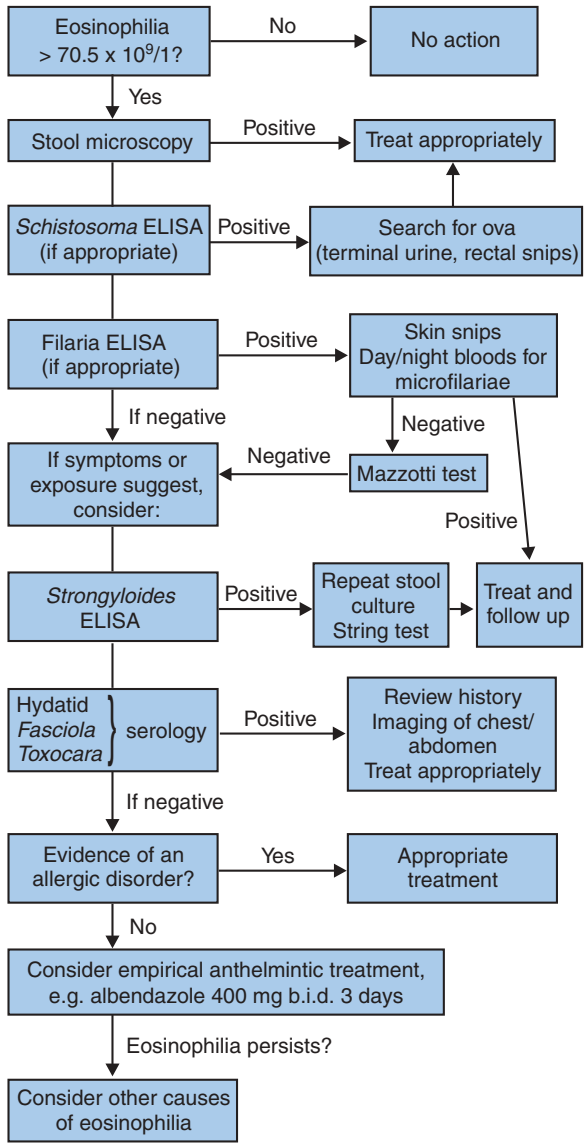

Figure 15.2 Approach to diagnosis of eosinophilia in returned travellers. (Modified from [120], with permission)

Post-travel check

Post-travel checks are frequently requested by travellers, although their usefulness remains controversial. These travellers usually fall into three groups: those concerned about specific risk exposures; those who have had unexplained illness in the tropics; and those who have been abroad but are otherwise well. The first two groups have had a risk exposure or an illness for which diagnosis and treatment could prevent possible future health problems, and further investigation is usually recommended. This includes patients at risk of relapse or late complications of incompletely treated malaria, borreliosis, amoebiasis, schistosomiasis, giardiasis and the filariases. The importance of sexually transmitted diseases has already been discussed. The third group may have unknowingly had a risk exposure while living under local conditions for a prolonged period of time, and it may be worthwhile screening them for subclinical tropical infections; however, there is no evidence that screening

asymptomatic long-term (usually considered more than 6 months) travellers is cost-effective.

Another category of asymptomatic patients who might benefit from screening include specific occupational groups such as food handlers or nursery workers who may have acquired infections that could be transmitted to others. The principles of screening individual travellers are somewhat different from instituting a public health-oriented screening programme for specific groups of people such as immigrants, refugees or other displaced persons, or for children arriving from overseas for adoption [121]. In these groups the spectrum of illnesses that are screened for are different and focused more on transmissible diseases such as tuberculosis and hepatitis B, for which specific prevention measures are available.

Some studies have described the prevalence of tropical infections in asymptomatic travellers and some have compared the cost-effectiveness of using different diagnostic screening strategies on asymptomatic travellers.

Prevalence of tropical diseases in asymptomatic returning travellers

In 1,029 British travellers (age range 8 months to 74 years) who had recently returned from the tropics (staying for 3 months to 45 years) and requested screening in London, one in four had an abnormality. Stool microscopy was positive for ova and cysts in 186/995 (19%); 67/852 (8%) had eosinophilia and in this group a parasitological cause was found in 26 (39%). Schistosomal serology was positive in 72/676 (11%) [122]. In a Dutch study, tropical diseases were diagnosed in 99/253 (39%) asymptomatic children returning from the tropics, of whom 58 (23%) had giardiasis and 19 (8%) had schistosomiasis [123]. In Montreal, 1,605 asymptomatic expatriates were screened and a parasitological diagnosis was found in 225 (17%) [124]. An Australian study found that of 221 travellers who visited East Africa, 117 (53%) considered themselves at risk for schistosomiasis and 10 (9%) were positive on subsequent testing [125].

Consequences of not detecting and treating parasites

The potential of untreated schistosomiasis or strongyloidiasis to cause serious problems has already been discussed, as has the importance of detection of asymptomatic Chagas' disease in order to reduce onward transmission. If HIV infection remains undetected the traveller will not benefit from chemoprophylaxis against opportunistic infections, or from specific antiretroviral therapy, and will be at risk of passing infection on to others. The consequences of untreated filariasis in the ordinary traveller are unclear and probably not significant. The majority of other intestinal parasites will eventually die without causing any harm to the host, and many feel that routine comprehensive travel screens of the asymptomatic patient are inappropriate for these reasons [126]. Moreover, screening will not reliably detect significant infections such as malaria and may lull the patient into a false sense of security. Meanwhile, the cost-effectiveness of routine post-travel screening has not been proven [128].

Screening methods

Nevertheless, it is common practice to offer screening to travellers who request it and a structured approach is required. A full travel and risk history should be taken. The extra information gained from a thorough physical examination is limited [128]. A full blood count should be examined, looking particularly for eosinophilia, together with stool microscopy for ova, cysts and parasites and specific culture for *Strongyloides* spp (but not for bacterial pathogens). The predictive diagnostic value of eosinophilia is reduced by its non-specific nature, so that a large number of investigations may be required. In our own experience and that of others [124], an eosinophil count $> 1 \times 10^9$/l is predictive of a parasitic infection in 40–50% of cases [107].

Patients who may have been exposed to schistosomiasis should be screened at least 3 months after departure. This is also a convenient time for discussion of HIV testing, as HIV seroconversion is likely to have occurred by then. If the tests are negative but there is strong concern, repeat screening at 6 months may be required for either of these infections. Other serological tests are of variable availability and cost, and we try to keep these to a minimum. However, adequate stool examination requires at least two, and ideally three, faecal specimens taken on different occasions (patients need specific instructions not to split one specimen three ways). This is time-consuming and expensive, but a study of 1,605 asymptomatic travellers showed that, in a Canadian setting, a combination of serological tests and up to three faecal examinations was more effective and cheaper than the combination of faecal microscopy and an eosinophil count for diagnosing schistosomiasis, filariasis and strongyloidiasis (89% versus 61% respectively) [124]. The cost-effectiveness balance will shift as more sensitive multiplex molecular methods become more widely available for the detection of faecal parasites [129].

Whatever the specific combination of tests used, patients who test negative need to be warned about the possibility of late appearance of malaria if they have been to a malarious area. They may need to be warned that travel to or residence in some parts of the world may be sufficient to bar them from being blood donors, even if they have no signs of past or current infection (Table 15.12).

Table 15.12 Some travel-related infections that may exclude the traveller from donating blood, either because of geographical exposure or past infection

African trypanosomiasis
American trypanosomiasis
Hepatitis B
Hepatitis C
HIV
HTLV-I/II
Malaria
New variant Creutzfeldt–Jakob disease
Visceral leishmaniasis

Finally, screening should explore non-infectious and situational problems, particularly in the 'worried well' or anxious patient. Reverse culture shock is a genuine problem for many travellers returning to their former western environment, and the healthcare worker should be attuned to the possibility of significant social or psychiatric problems [130]. This should be an integral part of the 'post-travel check', which, if it is to be performed at all, should not just be reduced to a couple of laboratory tests. In this context, family practice-based screening is likely to provide a more suitable environment than many busy hospital clinics. If for nothing else, the post-travel check-up should be seen as an opportunity for promoting healthy, safe behaviour next time the traveller ventures overseas.

Treatment versus screening

Alternative strategies are now being used to treat immigrant populations in some settings, based on the total costs (actual and projected) to the healthcare system. A study of refugees in New York concluded that presumptive treatment of all immigrants at risk for parasitosis with a broad-spectrum anthelmintic, such as albendazole, was cheaper and more effective than screening and treating, or waiting until clinical symptoms developed before treating. This policy prevented death and hospitalisation as well as saving money in the model used [131], and is specifically influenced by the prevalence and lifetime risk of undiagnosed strongyloidiasis [119]. This approach is recommended in the USA [132] but has not been widely adopted in the UK and is not generally suitable for individual returning travellers. It may have a role in special situations, for example empirical treatment of groups of travellers exposed to schistosomiasis by freshwater bathing in Africa, but the balance of risks and costs in this type of setting has not been modelled. Similar considerations have been extended to justify routine treatment of refugees for undiagnosed malaria as well as for intestinal parasites [133].

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References

1. United Nation World Tourism Organisation. Tourism highlights (2012) Available from: http://dtxtq4w60xqpw.cloudfront.net/sites/all/files/docpdf/unwtohighlights12enhr_1.pdf (accessed 17 October 2012).
2. Price VA *et al.* (2011) General physicians do not take adequate travel histories. *J Travel Med* **18**: 271–274.
3. Khuroo MS (2003) Viral hepatitis in international travellers: risks and prevention. *Int J Antimicrob Ag* **21**: 143–152.
4. Nielsen US *et al.* (2009) Hepatitis A among Danish travellers 1980–2007. *J Infect* **58**: 47–52.
5. Phillips-Howard PA *et al.* (1990) Risk of malaria in British residents returning from malarious areas. *BMJ* **300**: 499–504.
6. Barnett ED *et al.* (2010) The visiting friends or relatives traveller in the 21st century: time for a new definition. *J Travel Med* **17**: 163–170.
7. Schmetzer O (1999) Hemorraghic fever? Germany ex Cote D'Ivoire. ProMED Mail. Available from: http://www.healthnet.org/programs/promed.html (accessed 17 October 2012).
8. Beeching NJ *et al.* (2010) Travellers and viral haemorrhagic fevers – what are the risks? *Int J Antimicrob Ag* **36**: S26–S39.
9. Jacquerioz FA and Croft AM (2009) Drugs for preventing malaria in travellers. *Cochrane Database of Syst Rev*: Issue 4.
10. Memish ZA *et al.* (2012) Emergence of medicine for mass gatherings: lessons from the Hajj. *Lancet Infect Dis* **12**: 56–65.
11. Al-Abri SA *et al.* (2005) Traveller's diarrhoea. *Lancet Infect Dis* **5**: 349–360.
12. Hill DR and Beeching NJ (2010) Travellers' diarrhoea. *Curr Opin Infect Dis* **23**: 481–487.
13. Connor P *et al.* (2012) Diarrhoea during military deployment: current concepts and future directions. *Curr Opin Infect Dis* **25**: 546–554.
14. Bahn, MK *et al.* (2005): Typhoid and paratyphoid fever. *Lancet Infect Dis* **366**: 749–762.
15. Zignol M *et al.* (2011) Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007–2010. *Bull World Health Organ* **90**: 111–119D.
16. Ormerod P (2000) Tuberculosis and travel. *Hosp Med* **61**: 171–173.
17. Health Protection Agency (2013). Memorandum on Leprosy. Available from: http://www.hpa.org (accessed 17 October 2012).
18. Robson D *et al.* (2009) Consequences of captivity: health effects of Far East imprisonment in World War II. *QJM* **102**: 87–96.
19. Humar A and Keystone J (1996) Evaluating fever in travellers returning from tropical countries. *BMJ* **312**: 953–956.

20. Centers for Disease Control and Prevention and World Health Organization (1998) Infection Control for Viral Haemorrhagic Fevers in the African Health Care Setting. Atlanta: 1–198.
21. Harries AD *et al.* (1997) Practical and affordable measures for the protection of health care workers from tuberculosis in low-income countries. *Bull World Health Organ* **35**: 477–489.
22. Memish ZA and Osoba AO (2006) International travel and sexually transmitted diseases. *Travel Med Infect Dis* **4**: 86–93.
23. Hamlyn E *et al.* (2007) Sexual health and HIV in travellers and expatriates. *Occ Med* **57**: 313–321.
24. Vivancos R *et al.* (2010) Foreign travel, casual sex, and sexually transmitted infections: systematic review and meta-analysis. *Int J Infect Dis* **14**: e842–51.
25. Ford N and Inman M (1992) Safer sex in tourist resorts. *World Health Forum* **13**: 77–80.
26. Bellis MA *et al.* (2000) Ibiza uncovered: changes in substance use and sexual behaviour amongst young people visiting an international night-life resort. *Int J Drug Policy* **11**: 235–244.
27. Rogstad KE (2004) Sex, sun, sea, and STIs: sexually transmitted infections acquired on holiday. *BMJ* **329**: 214–217
28. Savage EJ *et al.* (2009) The European Surveillance of Sexually Transmitted Infections (ESSTI) network. Syphilis and gonorrhoea in men who have sex with men: a European overview. *Euro Surveill* **14**. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19417 (accessed 17 October 2012).
29. Rice B *et al.* (2012) Safe travels? HIV transmission among Britons travelling abroad. *HIV Med* **13**: 315–317.
30. Gavish I and Brenner B (2011) Air travel and the risk of thromboembolism. *Intern Emerg Med* **6**: 113–116.
31. Baltsezak S (2008) Clinic in the air? A retrospective study of medical emergency calls from a major international airline. *J Travel Med* **15**: 391–394
32. Dowdall N (2000) 'Is there a doctor in the aircraft?' Top 10 in-flight medical emergencies. *BMJ* **321**:1336–1337.
33. Leder K and Newman D (2005) Respiratory infections during air travel. *Intern Med J* **35**: 50–55.
34. Dowdall NP *et al.* (2010) Air travel and TB: an airline perspective. *Travel Med Infect Dis* **8**: 96–103.
35. Modi S *et al.* (2009) Reporting patterns and characteristics of tuberculosis among international travellers, United States, June 2006 to May 2008. *Clin Infect Dis* **49**: 885–891.
36. Minooee A and Rickman LS (1999) Infectious diseases on cruise ships. *Clin Infect Dis* **29**: 737–744.
37. Lim PL (2011) Influenza and SARS: the impact of viral pandemics on maritime health. *Int Marit Health* **62**:170–175.
38. Vivancos R *et al.* (2010). Norovirus outbreak in a cruise ship sailing around the British Isles: investigation and multi-agency management of an international outbreak. *J Infect* **60**:478–485.
39. Lyon RM and Wiggins CM (2010) Expedition medicine–the risk of illness and injury. *Wilderness Environ Med* **21**: 318–324.
40. Anderson SR and Johnson CJH (2000) Expedition health and safety: a risk assessment. *J R Soc Med* **93**: 557–562.
41. Department of Health (2012) Advisory Committee on Dangerous Pathogens. *Management of Hazard Group 4 viral haemorrhagic fevers and similar human infectious diseases of high consequence.* Available from: http://www.dh.gov.uk/health/files/2012/07/FINAL-VHF-guidance-for-publication.pdf (accessed 17 October 2012).
42. Centers for Disease Control and Prevention (2005) *Interim Guidance for Managing Patients with Suspected Viral Hemorrhagic Fever in US Hospitals.* Available from: http://www.cdc.gov/ncidod/dvrd/spb/pdf/vhf-interim-guidance.pdf (accessed 17 October 2012).
43. Torresi J and Johnson D (2011) Hepatitis A and E infection in international travellers. *Curr Infect Dis Rep* **13**:248–255.
44. Yagupsky P and Baron EJ (2005) Laboratory exposures to brucellae and implications for bioterrorism. *Emerg Infect Dis* **11**: 1180–1185.
45. Lettau LA (1991) Nosocomial transmission and infection control aspects of parasitic and ectoparasitic diseases Part II. Blood tissue parasites. *Infect Control Hosp Epidemiol* **12**: 111–121.
46. Owusu-Ofori AK *et al.* (2010) Transfusion-transmitted malaria in countries where malaria is endemic: a review of the literature from sub-Saharan Africa. *Clin Infect Dis* **51**:1192–1198.
47. Castro E (2009) Chagas' disease: lessons from routine donation testing. *Transfus Med.* **19**:16–23.
48. Communicable Disease Report (1997) Needlestick malaria with tragic consequences. *Communicable Disease Report Weekly* **7**(28).
49. Balkhy HH and Memish ZA (2003) Rift Valley fever: an uninvited zoonosis in the Arabian peninsula. *Int J Antimicrob Ag* **21**:153–157.
50. Trees A and Shaw S (1999) Imported disease in small animals. *In Practice: Journal of Veterinary Postgraduate Clinical Study*: 482–491.
51. Bernard SM and Anderson SA (2006) Qualitative assessment of risk for monkeypox associated with domestic trade in certain animal species, United States. *Emerg Infect Dis* **12**:1827–1833.
52. Gratz NG *et al.* (2000) Why aircraft disinfection? *Bull World Health Organ* **78**: 995–1003.
53. Nichols GL (2000) Food-borne protozoa. *Br Med Bull* **56**: 209–235.
54. Johnston V *et al.* (2009) British Infection Society and the Hospital for Tropical Diseases. Fever in returned travellers presenting in the United Kingdom: recommendations for investigation and initial management. *J Infect* **59**: 1–18.
55. Gautret P *et al.* (2009) GeoSentinel Surveillance Network. Multicenter EuroTravNet/GeoSentinel study of travel-related infectious diseases in Europe. *Emerg Infect Dis* **15**:1783–1790.
56. Bryceson ADM (1987) Imported fevers. *Advanced Medicine* **23**: 336–343 ed. Pounder RE & Chiodini PL. London: Bailliere Tindall.
57. Doherty JF *et al.* (1995) Fever as the presenting complaint of travellers returning from the tropics. *QJM* **88**: 277–281.
58. Harling R *et al.* (2004) Burden and cost of imported infections admitted to infectious diseases units in England and Wales in 1998 and 1999. *J Infect* **48**:139–144.
59. Wilson ME *et al.* (2007) Fever in returned travelers: results from the GeoSentinel Surveillance Network. *Clin Infect Dis* **44**: 1560–1568.
60. Carroll ED and Beeching NJ (2002) Fever in children returning from abroad. *Current Paediatrics* **12**: 534–544.
61. Hunziker T *et al.* (2012) Profile of travel-associated illness in children, Zürich, Switzerland *J Travel Med* **19**:158–162.

62. West N and Riordan FA (2003) Fever in returned travellers: a prospective review of hospital admissions for a 2(1/2) year period. *Arch Dis Child* **88**: 432–4
63. Ladhani S *et al.* (2010) Prospective, national clinical and epidemiologic study on imported childhood malaria in the United Kingdom and the Republic of Ireland. *Pediatr Infect Dis J* **29**: 434–438.
64. Maltha J and Jacobs J (2011) Clinical practice: the diagnosis of imported malaria in children. *Eur J Pediatr* **170**: 821–9
65. Smith AD *et al.* (2008) Imported malaria and high risk groups: observational study using UK surveillance data 1987–2006. *BMJ* **337**: a120.
66. Kain KC *et al.* (1998) Imported malaria: prospective analysis of problems in diagnosis and management. *Clin Infect Dis* **27**: 142–149.
67. Brabin BJ and Ganley Y (1997) Imported malaria in children in the UK. *Arch Dis Child* **77**: 76–81.
68. Checkley AM *et al.* (2012) Risk factors for mortality from imported falciparum malaria in the United Kingdom over 20 years: an observational study. *BMJ* **344**: e2116.
69. Svenson JE *et al.* (1995) Imported malaria: clinical presentation and examination of symptomatic travellers. *Arch Int Med* **155**: 861–868.
70. Bell D and Peeling RW (2006) Evaluation of rapid diagnostic tests: malaria. *Nat Rev Microbiol* **4**: S34–8.
71. McMorrow ML *et al.* (2011) Malaria rapid diagnostic tests in elimination settings – can they find the last parasite? *Clin Microbiol Infect* **17**:1624–3172.
72. Murray CK *et al.* (2005) Rapid diagnostic testing for malaria. *Trop Med Int Health* **8**: 876–883.
73. Jelinek T *et al.* (1999) Self-use of rapid tests for malaria diagnosis by tourists. *Lancet* **354**: 1609.
74. Rubio JM *et al.* (1999) Usefulness of seminested multiplex PCR in surveillance of imported malaria in Spain. *J Clin Microbiol* **37**: 3260–3264.
75. Cnops L *et al.* (2011) Validation of a four-primer real-time PCR as a diagnostic tool for single and mixed Plasmodium infections. *Clin Microbiol Infect* **17**:1101–1107
76. Mahajan B *et al.* (2012) Polymerase chain reaction-based tests for pan-species and species-specific detection of human Plasmodium parasites. *Transfusion* **52**:1949–1956.
77. Hanscheid T *et al.* (2000) Automated malaria diagnosis using pigment detection. *Parasitol Today* **16**: 549–551.
78. Teixeira MG and Barreto ML (2009) Diagnosis and management of dengue. *BMJ* **339**: b4338.
79. Leshem E *et al.* (2011) Travel-associated zoonotic bacterial diseases. *Curr Opin Infect Dis* **24**: 457–463.
80. European Centre for Disease Prevention and Control (2010) *Legionnaires'disease in Europe.* Available from: http://ecdc.europa.eu/en/publications/Publications/SUR-Legionnaires-disease-surveillance-2010.pdf
81. Guyard C and Low DE (2011) Legionella infections and travel associated legionellosis. *Travel Med Infect Dis* **9**:176–186.
82. Macneil A *et al.* (2011) Hantavirus pulmonary syndrome. *Virus Res* **162**: 138–147.
83. Swaminathan A *et al.* (2009) GeoSentinel Network. A global study of pathogens and host risk factors associated with infectious gastrointestinal disease in returned international travellers. *J Infect* **59**:19–27.
84. Svenungsson B *et al.* (2000) Enteropathogens in adult patients with diarrhoea and healthy control subjects: a 1-year prospective study in a Swedish clinic for infectious diseases. *Clin Infect Dis* **30**: 770–778.
85. Ramakrishna BS *et al.* (2006) Tropical malabsorption. *Postgrad Med J* **82**: 779.
86. Bain BJ (1996) Ethnic and sex differences in the total and differential white cell count and platelet count. *J Clin Pathol* **49**: 664–666.
87. Herbinger KH *et al.* (2012) Comparative study on infection-induced thrombocytopenia among returned travellers. *Infection* **40**:373–379.
88. Lalloo DG *et al.* (2007) UK malaria treatment guidelines. *J Infect* **54**:111–121
89. Centers for Disease Control and Prevention (2011) *Treatment of malaria: guidelines for clinicans (United States).* Available from: http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf (accessed 17 October 2012).
90. Sinclair D *et al.* (2012) Artesunate versus quinine for treating severe malaria. *Cochrane Database Syst Rev* **13**: 6.
91. Noedl H *et al.* (2008) Evidence of artemisinin-resistant malaria in western Cambodia. *NEngl J Med* **359**: 2619–2620.
92. Berkley J *et al.* (1999) Bacteraemia complicating severe malaria in children. *Trans R Soc Trop Med Hyg* **93**: 283–296.
93. Riddle MS *et al.* (2002) Exchange transfusion as an adjunct therapy in severe Plasmodium falciparum malaria: a meta-analysis. *Clin Infect Dis* **34**: 1192–1198.
94. Lalloo DG and Bell DJ (2010) Advances in the treatment of malaria. *Br J Hosp Med (Lond)* **71**: 246–247.
95. Price RN *et al.* (2009) New developments in Plasmodium vivax malaria: severe disease and the rise of chloroquine resistance. *Curr Opin Infect Dis* **22**: 430–435.
96. Maguire JD *et al.* (2007) Plasmodium vivax-associated acute respiratory distress syndrome after extended travel in Afghanistan. *Travel Med Infect Dis* **5**: 301–305.
97. Tjitra E *et al.* (2010) Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. *PLoS Med* **17**: e128.
98. Jacobs M (2000) Imported fever: A survival guide. *J R Soc Med* **93**: 124–128
99. Hay RJ (1993) Skin disease. *Br Med Bull* **49**: 440–453.
100. Caumes E *et al.* (1995) Dermatoses associated with travel to tropical countries: a prospective study of the diagnosis and management of patients presenting to a tropical disease unit. *Clin Infect Dis* **20**: 542–548.
101. Bouchaud O *et al.* (2000) Cutaneous larva migrans in travellers: a prospective study, with assessment of therapy with ivermectin. *Clin Infect Dis* **31**: 493–498.
102. Caumes E (2000) Treatment of cutaneous larva migrans. *Clin Infect Dis* **30**: 811–814.
103. Schwartz E *et al.* (2006). New world cutaneous leishmaniasis in travellers. *Lancet Infect Dis* **6**: 342–349.

104. Hepburn NC *et al.* (1993) Cutaneous leishmaniasis in British troops from Belize. *Brit J Dermatol* **128**: 63–68.
105. Bailey MS and Lockwood DN (2007) Cutaneous leishmaniasis. *Clin Dermatol* **25**: 203–211.
106. Whetham J *et al.* (2003) Investigation of tropical eosinophilia; assessing a strategy based on geographical area. *J Infect* **46**: 180–185.
107. Checkley AM *et al.* (2010) Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management. *J Infect* **60**:1–20
108. Ross AG *et al.* (2007) Katayama syndrome. *Lancet Infect Dis* **7**: 218–224
109. Cooke GS *et al.* (1999) Acute pulmonary schistosomiasis in travelers returning from Lake Malawi, sub-Saharan Africa. *Clin Infect Dis* **29**: 836–839.
110. Schwartz E *et al.* (2002) Hematospermia due to schistosome infection in travellers: diagnostic and treatment challenges. *Clin Infect Dis* **35**: 1420–1424.
111. Whitty CJ *et al.* (2000) Presentation and outcome of 1107 cases of schistosomiasis from African diagnosed in a non-endemic country. *Trans R Soc Trop Med Hyg* **94**: 531–534.
112. Harries AD and Cook GC (1987) Acute schistosomiasis (Katayama fever]: clinical deterioration after chemotherapy. *J Infect* **14**: 159–161
113. Blanchard TJ *et al.* (1993) Early chemotherapy of imported neuroschistosomiasis. *Lancet* **341**: 959.
114. Churchill DR *et al.* (1996) Clinical and laboratory features of patients with loiasis (Loa loa filariasis] in the UK. *J Infect* **33**: 103–109.
115. Hoerauf A *et al.* (2008) Effects of 6-week azithromycin treatment on the Wolbachia endobacteria of Onchocerca volvulus. *Parasitol Res* **103**: 279–286.
116. Specht S *et al.* (2008) Efficacy of 2- and 4-week rifampicin treatment on the Wolbachia of Onchocerca volvulus. *Parasitol Res* **103**: 1303–1309.
117. El-Beshbishi SN *et al.* (2012) Parasitic infections and myositis. *Parasitol Res* 2012 **110**: 1–18.
118. Centers for Disease Control and Prevention. (2012) Notes from the field: acute muscular sarcocystosis among returning travelers – Tioman Island, Malaysia, 2011. *MMWR Morb Mortal Wkly Rep* **61**:37–8.
119. Muennig P *et al.* (2004) The cost-effectiveness of ivermectin vs. albendazole in the presumptive treatment of strongyloidiasis in immigrants to the United States. *Epidemiol Infect* **132**:1055–1063.
120. Churchill DR *et al.* (1993) Screening the returned traveller. *Br Med Bull* **49**: 465–474.
121. Okereke E and Gellethe R (1999) Routine screening of children returning home from the tropics (letter). *BMJ* **319**: 121–122.
122. Carroll B *et al.* (1993) Post-tropical screening; how useful is it? *BMJ* **307**: 541–542.
123. Brouwer M *et al.* (1999) Routine screening of children returning home from the tropics: retrospective study. *BMJ* **318**: 568–569.
124. Libman MD *et al.* (1993) Screening for schistosomiasis, filariasis and strongyloidiasis among expatriates returning from the tropics. *Clin Infect Dis* **17**, 353–359.
125. Hipgrave DB *et al.* (1997) Schistosomiasis in Australian travellers to Africa. *Med J Aust* **166**: 294–297.
126. Conlon CP and Peto T (1993) Post-tropical screening (letter). *BMJ* **307**: 1008.
127. Genton B and Gehri M (1999) Routine screening of children returning home from the tropics (letter). *BMJ* **319**: 121.
128. Whitty CJ *et al.* (2000) Utility of history, examination and laboratory tests in screening those returning to Europe from the tropics for parasitic infection. *Trop Med Int Health* **5**: 818–823.
129. van Lieshout L and Verweij JJ (2010) Newer diagnostic approaches to intestinal protozoa. *Curr Opin Infect Dis* **23**: 488–493.
130. Lankester T (2000) Health screening and psychological considerations in the returned traveller. In *Travel Medicine and Migrant Health* . 443–452. eds C Lockie et al, Churchill Livingstone, Edinburgh
131. Muennig P *et al.* (1999) The cost effectiveness of strategies for the treatment of intestinal parasites in immigrants. *N Engl J Med* **340**: 773–779.
132. Centers for Disease Control and Prevention (2012) *Immigrant and refugee health. Overseas refugee health guidelines: intestinal parasites.* Available from: http://www.cdc.gov/immigrantrefugeehealth/guidelines/overseas/intestinal-parasites-overseas.html
133. Miller J M *et al.* (2000) Malaria, intestinal parasites and schistosomiasis among Barawan Somali refugees resettling to the United States: a strategy to reduce morbidity and decrease the risk of imported infections. *Am J Trop Med Hyg* **62**: 115–121.

Further reading

Australian Society for Infectious Diseases (2009) *Diagnosis, management and prevention of infections in recently arrived refuges*. Sydney, Dreamweaver Publishing Pty Ltd. Available from: http://www.asid.net.au/Clinical-Guidelines.

Cohen J *et al.* (2010) *Infectious Diseases*, 3rd edition. Elsevier Science, London.

Farrar J *et al.* (2013) *Manson's Tropical Diseases* 23rd edn, Saunders/ Elsevier Science, London.

Feigin RD *et al.* (2009) *Textbook of Pediatric Infectious Diseases*, 6th edn. Elsevier. London.

Guerrant RL *et al.* (2011) *Tropical Infectious Diseases: Principles, Pathogens and Practice*, 3rd edn. Churchill Livingstone, Philadelphia.

Magill AJ *et al.* (2012) *Hunter's Tropical Medicine and Emerging Infectious Diseases*, 9th edn. Saunders/ Elsevier Science, London.

Keystone JS *et al.* (2013) *Travel Medicine*, 3rd edn. Mosby/Elsevier.

Lockie C *et al.* (2000) *Travel Medicine and Migrant Health*. Churchill Livingstone, Edinburgh.

Peters W and Pasvol G (2007) *Atlas of Tropical Medicine and Parasitology*, 6th edn. Elsevier London.

Mandell GL *et al.* (2010) *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th edn. Churchill Livingstone/Elsevier, Oxford.

Walker P and Barnett E (2007) *Immigrant Medicine*. Elsevier, London.

Schwartz E (2009) *Tropical Diseases in Travellers*. Wiley Blackwell, Chichester UK.

Additional resources

Non-subscription English language websites giving useful geographically oriented medical information

British Foreign and Commonwealth Office Travel Warnings; http://www.fco.gov.uk/en/. Country specific safety information.

Centers for Disease Control and Prevention (CDC) Travellers' Health; http://www.cdc.gov/travel/ Regional specific database for recommended immunisations and malaria prevention. Also includes international outbreaks.

European Surveillance; http://www.eurosurveillance.org/ Weekly and monthly European surveillance information.

Fitfortravel; http://www.fitfortravel.nhs.uk/home.aspx Health Protection Scotland's website with country specific and general travel health information and alerts. User friendly for travelling public

Fever Travel; www.fevertravel.ch Useful resource including guidelines and algorithms for evaluation of fever in returning travelers or migrants.

GIDEON Web; www.GIDEONonline.com Based on a long established database on infections worldwide (requires subscription)

Global Alert and Response (GAR) Outbreak Information (WHO); http://www.who.int/csr/don/en/ Regular reports on WHO-confirmed outbreaks of international importance.

International Society of Travel Medicine; http://www.istm.org/ index.html Current news and conference information. Listing of travel clinics worldwide. Electronic interaction of health care professionals via Travelmed forum.

International Health Regulations (WHO); http://www.who.int/topics/international_health_regulations/en/ Country specific yellow fever requirements and malaria recommendations. Updated annually.

National Travel Health Network and Centre (NaTHNaC); http://www.nathnac.org/ Evidence based UK website with detailed country information and regular travel health alerts. General and specific information for travellers and health care workers

ProMED-Mail; http://www.promedmail.org/ Regular, early reports on international outbreaks, with short commentaries. Archived in several languages. A programme of the International Society for Infectious Diseases.

US State Department Travel Warnings; http://travel.state.gov/ US State Department travel warnings and consular information sheets.

Weekly Epidemiological Record (WHO); http://www.who.int/wer/ Weekly report on infections from WHO.

World Health Organization (WHO); http://www.who.int/ Good information source for worldwide communicable and noncommunicable disease.

Section IV
Hazards of air and sea travel

Chapter 16 Aviation medicine

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Essentials

- Travel by air is a safe means of transport. However, from the physiological point of view, flying is a means of putting people at risk as well as a potential means of spreading infectious disease.
- Atmospheric pressure falls with altitude, the percentage of oxygen remaining constant at about 21%. Alveolar partial pressure determines the amount of oxygen available for combination with haemoglobin. Above about 10,000 feet blood desaturation leads to hypoxia.
- Epidemiological evidence indicates that the probability of airline crew members or passengers suffering abnormality or disease as a result of cosmic radiation is very low.
- There is no simple solution for combating the effects of jet lag. The individual must evolve strategies to suit their particular needs.
- While the relative risk of developing venous thrombosis when flying is significant, the absolute risk of developing symptomatic DVT is very low. The absolute risk of developing a pulmonary embolus during or after a flight between the UK and the US has been calculated as less than 1 in a million. Medical practitioners need to be circumspect in advising preventive measures, taking careful account of efficacy and risk profile of the preventive method.
- Guidance for assessing a passenger's fitness to fly is provided by the websites of the Aerospace Medical Association and the British Thoracic Society.
- There is no evidence that the pressurised cabin itself makes transmission of disease any more likely, and it has been shown that recirculation of cabin air is not a risk factor for contracting symptoms of upper respiratory tract infection.
- Restricting air travel will not prevent global spread of pandemic influenza, but might delay the spread sufficiently to allow countries time to prepare.
- It is important that individuals should not travel on commercial aircraft with a febrile illness.

Introduction

Aviation medicine is a branch of occupational medicine that has developed from human needs to adapt to the inherently hostile environment of the air. It is a wide-ranging discipline, encompassing physiological and psychological aspects of fitness to fly, and the human factors facets of flight safety are recognised as an important component of flight crew training. The normal physiology of the human body when in flight can be influenced by altitude, changes in pressure, temperature, acceleration and sensory perception. This chapter is concerned only with those areas of aviation medicine applicable to travel medicine. For fuller consideration of the wider discipline, the reader is referred to more comprehensive texts listed in Further reading.

Commercial air travel is a comfortable, speedy and safe means of transport and is accepted as a part of everyday life for many people in the developed world. It is affordable and accessible to almost all sectors of the population, but it is easy to forget that the individual is travelling in a potentially physiologically hostile environment.

The atmosphere

Physics of the flight environment

The earth's atmosphere is an oxygen-rich gas that shields the ground below from solar radiation above. Held to the earth by gravity, compressed under its own weight, the atmosphere is denser close to the ground than further away. Long waves of infrared light penetrate it easily and heat the ground below. Hot ground reradiates some of this heat at shorter wavelengths which are absorbed by carbon dioxide and water vapour, making the air close to the ground much warmer than that higher up. Short waves of ultraviolet sunlight, absorbed by oxygen molecules early in their journey,

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create a belt of warm ozone at high altitudes. Some rays intercepted in the same region generate secondary rays that extend lower down. Very few reach the ground. At sea level the atmosphere exerts a pressure of about 760 mmHg (101 kPa); it is variably moist, has a temperature that ranges from −60°C to +60°C, and moves at wind speeds from 0 to 160 km/h. With increasing altitude, the temperature, pressure and water content of the atmosphere fall and wind speeds increase. The International Standard Atmosphere defines sea level pressure as 760 mmHg, temperature 15°C and temperature lapse rate of 1.98°C per 1,000 feet of ascent.

Atmospheric pressure

Total gas pressure falls with altitude in a regular, almost exponential way, halving every 18,000 ft (5,500 m). The oxygen content of the atmosphere (20.93%) is constant to very high altitudes. The oxygen pressure of physiological importance is that which exists in ambient air when it is warmed and wetted on entering the bronchial tree. This process necessarily raises water vapour pressure to about 47 mmHg, regardless of the total gas pressure outside. The oxygen pressure in moist inspired gas (PiO_2) fully saturated with water vapour at 37°C is given by the relationship:

$$PiO_2 = FiO_2 (PB - 47)$$

where FiO_2, the fractional concentration of oxygen in the inspirate, is 0.2093 when air is inspired.

Atmospheric temperature

Atmospheric temperature drops more or less linearly with altitude, at about 2°C/1,000 ft (300 m), to the tropopause (40,000 ft [12,200 m]), is stable at −56°C up to about 80,000 ft (24,400 m) and then rises to almost body temperature at about 150,000 ft (46,000 m), but by then air density is so low that its temperature is unimportant (cf. the dense cold air below).

Atmospheric ozone

Atmospheric ozone is formed by irradiation of diatomic oxygen molecules which dissociate into atoms. At very high altitudes the ultraviolet irradiation is so intense that all oxygen exists in the monatomic form. Lower down, some of the monatomic oxygen produced at higher levels combines with oxygen molecules to form the triatomic gas O_3 (ozone), at concentrations from 1 to 10 parts per million (ppm). The ozonosphere normally exists between 40,000 and 140,000 ft (12,200 and 42,700 m), i.e. from one-fifth to one-thirtieth of an atmosphere. Below 40,000 ft (12,200 m) the irradiation is normally too weak for significant amounts of ozone to form. Concentrations of 1 ppm at sea level cause lung irritation. Ten times that concentration can cause fatal lung oedema. Although the ozonosphere is at much lower pressure, the ventilation systems of aircraft flying at very high altitudes can take in the ozone and compress it to partial pressures at which pulmonary irritation is a potential hazard. However, modern passenger jet aircraft are fitted with catalytic converters in the environmental control system which break down the ozone before it enters the pressurised cabin.

Cosmic radiation

Aircraft occupants are exposed to elevated levels of cosmic radiation of galactic and solar origin. The intensity of the different particles making up atmospheric cosmic radiation, their energy distribution and their potential biological effects vary with altitude, geomagnetic latitude and the point of time in the sun's magnetic activity cycle.

The sun has a varying magnetic field, which reverses direction approximately every 11 years. Near the reversal, at 'solar minimum', there are few sunspots and the sun's magnetic field extending throughout the solar system is relatively weak. At solar maximum there are many sunspots and other manifestations of magnetic turbulence.

When the solar magnetic field is stronger, less galactic cosmic radiation reaches the earth. Thus solar maximum causes a radiation minimum and, conversely, solar minimum is at the time of radiation maximum. At commercial jet aircraft operating altitudes, the ratio for galactic cosmic radiation at solar minimum to that at solar maximum is about 1.2:2 and increases with altitude.

The earth's magnetic field has a larger effect than the sun's magnetic field on cosmic radiation approaching the atmosphere. The protective effect is greatest at the equator and least at the magnetic poles. At jet aircraft operating altitudes, galactic cosmic radiation is 2.5 to 5 times more intense in polar regions than near the equator.

The earth's surface is shielded from cosmic radiation by the atmosphere, the ambient radiation decreasing with altitude by approximately 15% for each increase of around 2,000 ft (dependent on latitude) [1].

As well as providing shielding from galactic cosmic radiation, the atmosphere contributes different components to the radiation flux as a function of atmospheric depth. The total effective dose rate at 30,000 ft is about 90 times the rate at sea level, with neutrons being the dominant component above 10,000 ft.

Solar flares

About once per year a solar particle event (SPE) occurs, causing an observable increase in the intensity of the cosmic

radiation field at commercial jet aircraft operating altitudes. Since 1956, no event has presented any risk of attaining an annual dose of 1 milliSievert (mSv) (the recommended public exposure limit).

Disruption of long distance radio communications and activity of the aurorae borealis and australis (northern and southern lights) are not an indication of increased ionising radiation levels at flight altitudes.

Protection against effects of cosmic radiation

The International Commission on Radiological Protection (ICRP) recommended in 1991 that exposure of flight crew members to cosmic radiation in jet aircraft should be considered part of occupational exposure to ionising radiation.

In 1994, the USA Federal Aviation Administration (FAA) recommended that air carrier aircrews should be informed about their radiation exposure and associated health risks, and that they be assisted in making informed decisions with regard to their work environment.

In Europe, the Council of the European Union (EU) adopted a directive laying down safety standards for the protection of the health of workers and the general public against the effects of ionising radiation, and this was applied to aircrew with effect from May 2000

Both the FAA and the EU apply the ICRP limits for occupational exposure of a 5-year average effective dose of 20 mSv per year, with no more than 50 mSv in a single year.

Cosmic radiation doses

The effect of ionising radiation depends not only on the dose absorbed, but also on the type and energy of the radiation and the tissues involved. These factors are taken into account in arriving at the dose equivalent measured in Sieverts (Sv). However, doses of cosmic radiation are so low that figures are usually quoted in microsieverts (μSv; millionths of a Sievert) or millisieverts (mSv; thousandths of a Sievert).

For flight operations in the northern hemisphere, mean ambient equivalent dose rates have been measured in the region of:

- long-haul: 4–5 μSv per hour
- short-haul: 1–3 μSv per hour.

In general, for UK-based crew members operating to the maximum flight time limitations, it is calculated that:

- long-haul crew have an annual mean effective exposure of 2–3 mSv per year, i.e. less than one-fifth of the ICRP recommended dose limit
- short-haul crew have an annual mean effective exposure of 1–2 mSv per year, i.e. less than one-tenth of the recommended dose limit [1].

For ultra-long-range airline operations (arbitrarily defined as sector lengths in excess of 18 hours), recent studies [2] have shown a mean effective sector exposure of 80 μSv on the Dubai to Los Angeles route. A crew member flying three return trips per month would accrue an annual exposure of 5.76 mSv.

For passengers, the ICRP limit for the general public of 1 mSv per year equates to about 200 hours per year on trans-equatorial subsonic routes [3].

There are essentially two types of airline passenger – the occasional social traveller and the frequent business traveller. The public limit of 1 mSv per year will be of no consequence to the former, but could be of significance to the frequent business traveller who would exceed the 1 mSv limit if flying more than eight transatlantic or five UK–Antipodean return subsonic journeys per year [3]. However, business travellers are exposed to radiation as an essential part of their occupation and it is logical to apply the occupational limit of 20 mSv to this group. This view has the support of the ICRP [4].

Health risks of cosmic radiation

While it is known that there is no level of ionising radiation exposure below which effects do not occur, all the current epidemiological evidence indicates that the probability of airline crew members or passengers suffering any abnormality or disease as a result of exposure to cosmic radiation is very low.

Oxygen requirements at altitude

Respiration and circulation

Respiration is essentially the process by which organisms such as humans liberate energy to maintain the processes of life by oxidation of food. For convenience it may be divided into three phases.

1 The exchange of gases between body and atmosphere.
2 The carriage of gases to and from the reservoir (the lungs) and the site of oxidation (the tissue cells).
3 The actual oxidative process at cellular level, liberating energy.

Aviation can profoundly affect the first two, but has little or no effect on the third.

Gaseous exchange

The oxygen used in the energy liberation is obtained from atmospheric air. This enters the body via the nasopharynx

and passes down the trachea into one of the lungs via the appropriate bronchus and bronchioles, ending in an alveolus, millions of which form the lungs.

The mechanism of the gas flow is simple. The lungs, which communicate fully with the atmosphere, lie in the thoracic cavity, which is bounded by the rib cage and diaphragm. As the thorax is a closed cavity, any change in its volume causes a corresponding change in lung volume. Inspiration is the act of diaphragm contraction and elevation of the ribs using the intercostal muscles, thereby increasing lung volume and drawing in air (an active process). Expiration is a reverse of this process, relaxing the diaphragm and intercostal muscles, decreasing the lung volume and driving out air (a passive process). The rate and depth of respiration are controlled by the metabolic demands of the tissues in their need for oxygen and elimination of the waste products carbon dioxide and water vapour. These can vary enormously, depending on the state of activity of the body. At rest, each breath involves about half a litre of air, and the cycle occurs 12–15 times a minute.

As stated previously the atmospheric air ends in the alveolae or air sacs. An alveolus is a very thin-walled structure covered with a complex of capillaries or small blood vessels that brings the blood within the closest possible apposition to the lung air. Here, diffusion takes place; oxygen from the lung air diffuses across the thin barrier of alveolar and blood vessel walls to enter the blood, and the waste products of cellular respiration carried by the blood to the lung diffuse from the blood into the air sac.

Carriage of gases

Oxygen diffusing across the alveolar wall into the closely apposed blood is carried to its ultimate destination in chemical combination with haemoglobin, a component of the red blood cell (erythrocyte). A very small proportion of oxygen is carried in physical solution. The circulatory path is as follows.

1 Blood leaves the lungs and returns to the left side of the heart, from where it is pumped in arteries to the tissues of the body.

2 Here oxygen diffuses into the cells and is used in the oxidative processes. Energy is released, with the consequent production of carbon dioxide and water.

3 These waste products thence diffuse back into the bloodstream and are ultimately carried back to the right side of the heart via the venous system.

4 From here the blood is pumped to the lungs, where gaseous exchange occurs in the alveoli.

Despite the embolic inference of the description it must be understood that the whole is one continuous, flowing process. The path of oxygen to the tissues and that of carbon dioxide from the tissues may be summarised as follows.

- Oxygen pathway in the body: atmosphere → trachea → bronchi → alveoli → blood → tissue.
- Carbon dioxide pathway in the body: tissue → blood → alveoli → bronchi → trachea → atmosphere.

Control of respiration

The rate and depth of breathing is controlled by the metabolic demands of the tissues. The fundamental controlling factor is the partial pressure of carbon dioxide (PCO_2) in the blood perfusing the respiratory centre in the brain. This is extremely sensitive to small changes in the carbon dioxide tension in the blood, and continuously adjusts the breathing rate to maintain this tension at a normal level. The receptors in the respiratory centre are also sensitive to the acidity of the arterial blood. Another set of chemoreceptors is located in the carotid arteries and these also respond to changes in the tension of carbon dioxide in the arterial blood by influencing the breathing rate. In addition, these carotid receptors are very sensitive to reduction in arterial oxygen tension.

Composition of alveolar air

The composition of alveolar air differs from that of atmospheric air due to the constant diffusion of gases to and from the alveolus and the blood.

While the total pressure is the same, the composition is different. Unlike the ambient atmospheric air, alveolar air includes water vapour and carbon dioxide generated by the body, which remains as a constant, provided the respiratory rate remains constant and the body at rest. As the total pressure has remained the same, to accommodate the water vapour and carbon dioxide the pressures of oxygen and nitrogen must be reduced. For a healthy young individual at sea level, the total pressure of 760 mmHg is the sum of N_2 570 + O_2 103 + CO_2 40 + H_2O 47 mm Hg.

It may be observed that human beings' apparent efficiency deteriorates but little during ascent from sea level. Despite a fall in atmospheric pressure and consequent reduction in oxygen pressure in the lung, they remain reasonably efficient to an altitude of about 10,000 feet (3,000 m). Above 10,000 feet (3,000 m), however, the oxygen tension falls below a critical level and deterioration in performance becomes obvious.

To prevent this deterioration when flying, a method of augmenting the oxygen content of the respired air has to be found such that, by gradual displacement of nitrogen, the alveolar oxygen tension is not allowed to fall below the ideal level of 103 mmHg. This can be done by supplying oxygen

from a source through a mask to the subject's respiratory tract with increasing concentration, such that the inspired mixture has the correct amount of oxygen to maintain a partial pressure of oxygen of 103 mmHg in the lung. An alternative method is to pressurise the aircraft cabin with engine-bleed air, or via an electrical compressor, to give an effective altitude of less than 10,000 feet (3,000 m).

The oxygen dissociation curve

The ability of the normal healthy individual to function efficiently up to an altitude of approximately 10,000 feet (3,000 m) is explained by the relationship between the oxygen saturation of haemoglobin and oxygen tension. Ascent to an altitude of 10,000 feet (3,000 m) produces a fall in the partial pressure of oxygen in the alveoli but only a slight fall in the percentage saturation of haemoglobin with oxygen. However, once altitude rises above 10,000 feet (3,000 m) the percentage saturation of haemoglobin falls quickly, resulting in the condition of hypoxia. In fact, above 8,000 feet (2,400 m) the effects of lack of oxygen will begin to appear and a decrease in the individual's ability to perform complex tasks and a reduction in night vision can be measured.

Figure 16.1 shows the oxygen dissociation curve of blood, with the concentrations of physically dissolved and chemically combined oxygen being shown separately. The curve illustrated is the average for a fit young adult. The actual shape of the curve will be influenced by factors such as age, state of health, tobacco abuse and ambient temperature.

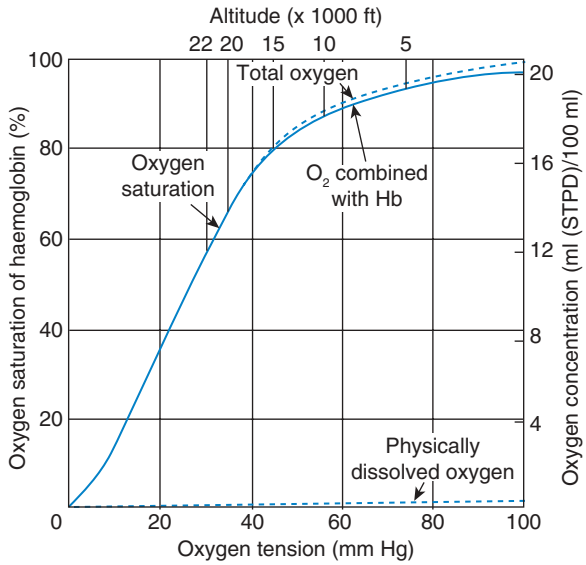

Figure 16.1 The oxygen dissociation curve of blood.

Hypoxia and hyperventilation

Hypoxia

This is the term used to denote the body condition when the oxygen available to the tissues is insufficient to meet their needs and will become obviously manifest when the partial pressure of oxygen in the lungs falls below about 55 mmHg. The tissues of the body become deprived, each becomes less efficient, but by far the most sensitive and susceptible is the brain. Consequently the first symptoms experienced by the hypoxic individual will be those resulting from brain inefficiency. The symptoms are in general terms similar in everybody, but have minor variations in individuals.

The classical symptoms of hypoxia may be summarised as follows.

1 *Personality change.* This is the initial stage of hypoxia. It is characterised by a change in the person's outlook, and their normal inhibitive forces of common sense tend to be diminished.

2 *Impaired judgement.* Loss of self-criticism, euphoria or depression. This stage can be particularly dangerous for air crew, as, far from realising something is wrong, the air crew member may well be led into a false state of wellbeing, which may lead on to a careless, carefree attitude, with reckless behaviour.

3 *Mental and muscular incoordination.* This is the stage of finding difficulty in 'thinking straight'. Constructive, progressive, logical thought processes become difficult, while coordinated muscular movements, such as clear speech or writing, become impaired.

4 *Sensory loss.* Concomitantly, inputs to the body via the sense organs are also diminished, thus such things as vision, hearing and the sense of touch become impaired.

5 *Memory impairment.* A classical symptom of hypoxia is impairment of recall for recent events, and is in the main due to difficulty in structuring thought. Obviously this is a most important effect for air crew to be aware of, as an unimpaired memory is imperative for recall of vital actions necessary to remedy the situation by previously taught emergency drills. Fortunately this is a fairly late symptom, and provided the air crew member has absorbed previous training, they should have spotted the predicament before this potentially catastrophic stage is reached.

6 *Loss of consciousness.* Following memory loss, impairment of consciousness followed by loss of consciousness supervenes, leading ultimately to death.

The above are symptoms experienced or felt. Other signs are directly observable.

1 *Cyanosis.* This is due to low oxygen concentration in the blood. As a consequence the complexion takes on a bluish

hue, the skin becoming dusky, and fingernails and lips in particular become blue, similar to the colour of the hands on a cold day.

2 *Hyperventilation.* Low oxygen tension in the blood will lead to 'air hunger', manifested by more frequent or deeper breathing. There may be other causes of excessive breathing, but above 10,000 feet the probability of hypoxia as a cause of hyperventilation should always be considered.

Factors increasing susceptibility to hypoxia

- *Exercise.* Any increase in physical activity will increase oxygen consumption.
- *Cold.* Cold will induce an increase in the body metabolism, thus increasing oxygen consumption.
- *Ill health.* Any illness or intercurrent infection will probably induce increased need for oxygen, thereby lowering the threshold for hypoxia.
- *Fatigue.* While fatigue may not increase the need for oxygen, the threshold for hypoxia is lowered.
- *Drugs.* The dulling of the senses induced by some drugs, in particular cold cures, and the lowering of one's wellbeing following alcohol consumption, no doubt lowers the tolerance to hypoxia.
- *Smoking.* Carbon monoxide, as produced by smoking, has a much greater affinity for haemoglobin than oxygen. Thus less oxygen is carried, increasing susceptibility to hypoxia.

Hyperventilation

Hyperventilation may be defined as breathing in excess of the metabolic needs of the body. As a consequence, the level of carbon dioxide in the blood is lowered, while by definition it is not being replaced by carbon dioxide produced as a result of metabolic processes.

It can be seen from this definition that a man breathing heavily following exertion has increased his metabolism. He needs more oxygen and has produced more carbon dioxide. Consequently the rate and depth of breathing is not in excess of his needs. Conversely, an individual breathing in excess without accompanying activity cannot take in extra oxygen, and does not produce extra carbon dioxide. The excessive breathing will remove carbon dioxide from the bloodstream faster than metabolic production, thereby lowering blood carbon dioxide level, leading to a change in blood acidity. This will lead to symptoms which in themselves can be alarming.

Factors that induce hyperventilation

- *Stress.* In circumstances that threaten the perceived wellbeing of an individual, certain reactions take place in the body which prepare it for physical activity, anticipating its struggle for survival. In the past this meant either fighting or fleeing. In either case, great muscular activity would take place, consuming more oxygen and producing more carbon dioxide. Therefore, part of this preparatory reaction entails deeper breathing. However, should the extra physical activity not take place, the extra carbon dioxide will not be produced and the increased breathing would be in excess of the body needs, i.e. hyperventilation would occur leading to the condition known as hypocapnia.
- *Hypoxia.* Whereas the normal stimulation for the waxing and waning of respiration is the level of blood carbon dioxide, any significant fall in the availability of oxygen will override this and hypoxia immediately stimulates both rate and depth of breathing. This in turn obviously lowers the blood carbon dioxide, precipitating symptoms of hyperventilation.
- *Vibration.* Whenever whole body vibration is experienced, respiration is stimulated, and if severe enough results in hyperventilation symptoms.
- *Hyperventilation syndrome.* Whereas in general medicine, the hyperventilation syndrome may not always be readily recognised as a clinical entity, falling as it does between physiology, psychiatry, psychology and medicine, the condition of hyperventilation is readily accepted in aviation medicine. An acute episode of hyperventilation, such as might occur in response to an emergency, leads to symptoms that are misdiagnosed or incorrectly diagnosed. The symptoms can be alarming and as a consequence, the individual's anxieties are increased and further consultation sought, leading to perpetuation of the disorder, as shown in Figure 16.2.

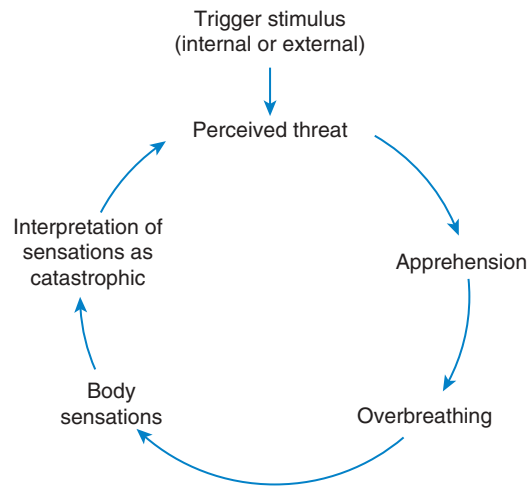

Figure 16.2 The hyperventilation syndrome.

Symptoms

The symptoms of hyperventilation are classical and may be summarised as follows.

- *Dizziness.* Shortly after the onset of hyperventilation it is common for most people to experience a giddy or dizzy sensation.
- *Tingling and cramp.* Tingling of the extremities (hands, feet) or face may be felt and, in extreme cases, peripheral muscular paralysis (tetany) may occur.
- *Visual disturbances.* Many people experience a clouding or dimming of vision, perhaps accompanied by palpitations and hot flushes, which in turn generates further anxiety.
- *Disturbed consciousness.* It is possible in a severe attack for the symptoms to progress to clouding of consciousness and ultimately loss of consciousness; however, this is followed by immediate recovery as the respiratory rate returns to normal.

Effects of reduced atmospheric pressure

By Boyle's law, the pressure of any gas is inversely related to its volume, providing the temperature remains constant. Hence, in aviation, where the body temperature remains essentially constant, when we ascend to altitude, gas trapped anywhere in the body will tend to expand as altitude increases and atmospheric pressure decreases. The problems thus produced are known as 'trapped gas dysbarism'.

In addition, gas that is dissolved in the tissues and body fluids at sea-level pressures may come out of solution in the form of bubbles as the pressure reduces with altitude, in accordance with Henry's law. The problems associated with this phenomenon are known as 'evolved gas dysbarism' and the gas of concern is nitrogen. When these nitrogen bubbles form in the tissues they give rise to a condition known as decompression sickness.

Trapped gas dysbarism

The body cavities that contain gas are as follows.

Middle ear Many air travellers are familiar with what happens when they cannot clear their ears as a result of a common cold. The mechanism of this disturbance, known as otic barotrauma, may be explained as follows.

The eustachian tube connects the middle-ear cavity with the nose. It permits the passage of air in and out of the middle-ear cavity, thus preventing distortion of the eardrum during changes in ambient pressure. The normal state of the tube is collapsed, similar to a bicycle tyre inner tube that is not inflated, where the lower half of the tube passes through the soft tissues behind the nose. During ascent, the expanding air in the middle-ear cavity escapes easily down the tube. On descent, however, the increasing pressure may cause difficulty with re-entry of air to the middle ear due to swollen mucous membranes and congestion around the opening of the tube behind the nose. Normally, the tube can be opened voluntarily by manoeuvres such as yawning or swallowing. In the event of congestion of membranes lining the nose and throat, the lining of the tube becomes swollen and may not open. The unequal pressures so produced cause the eardrum to be drawn inwards, resulting in pain, deafness, and possible dizziness and disorientation. In the worst case, the eardrum may perforate. Ideally one should not fly with a cold or other forms of upper respiratory congestion, such as hay fever. If travel is essential, frequent steam inhalation on the days preceding travel plus the judicious use of a nasal decongestant spray (e.g. oxymetazoline or xylometazoline) may prevent the development of barotrauma.

Sinuses The sinuses are cavities in the bones of the face that open into the nose. They are situated above the eyes, in the cheeks and at the back of the nose. Like the middle ear, no problems are usually encountered on ascent, but on descent, if their openings into the nose become blocked by a cold or catarrh preventing air entry, the relative vacuum created in the cavities will cause damage to their lining membranes. This leads to inflammation and bleeding within the sinus cavities, which may produce pain, often severe, and frequently nose bleeding. This condition of pressure effect on the sinuses is known as sinus barotrauma.

Gut Ascent to 18,000 feet (5,500 m) from ground level halves the atmospheric pressure and therefore doubles the volume of gas trapped in the stomach and in the intestines. Normally this is voided quite easily. but occasionally, when ascent is fairly rapid, it can cause discomfort or pain. Avoidance of gas-forming foods, such as curries, beans, etc., can minimise these effects.

Teeth Any tooth that has been filled recently has a small quantity of air trapped underneath the filling. Usually, this air escapes around the edge of the filling when its owner goes to altitude. Occasionally, however, the air does not escape and, on ascent, it causes pressure on the nerve of the tooth, resulting in pain. Similar pain can be caused by gas produced in dental decay. This is known as barodontalgia.

Lungs If a sudden decompression is rapid enough and over a big enough pressure range, damage to the lungs is theoretically possible. Such high rates of pressure change could occur when a large defect is suddenly produced in a high-differential

pressure cabin. However, in an aircraft with a cabin altitude of 8,000 feet (2,400 m), decompression resulting from the loss of a window, even at very high altitude, has not been known to cause lung damage.

Decompression sickness

Decompression sickness is a condition that can arise as a result of exposure of the body to reduced atmospheric pressure either in an aircraft or in a decompression chamber. It is rare below 25,000 feet (7,600 m), but the incidence and onset increases rapidly above this altitude.

Causes

The human body is saturated with nitrogen, which is in solution in tissues and body fluids, at a partial pressure of gas equal to that of the surrounding atmosphere. When the ambient pressure is lowered, the nitrogen tends to come out of solution. The formation of nitrogen bubbles thus released from solution is generally accepted as the cause of decompression sickness.

The following factors increase susceptibility to decompression sickness.

- *Altitude.* Decompression sickness rarely occurs below 18,000 feet (5,500 m) cabin altitude, is unlikely below 25,000 feet (7,600 m) and the incidence increases with altitude above this level.
- *Duration of exposure.* The longer the exposure, the greater the number of individuals affected by decompression sickness.
- *Re-exposure.* Re-exposure to altitude, within 48 hours, increases susceptibility to decompression sickness.
- *Exercise.* Exercise while at altitude is one of the most important factors influencing susceptibility to this condition. There is also evidence that pre-flight exercise may increase the incidence of decompression sickness.
- *Temperature.* Cold may increase the incidence of decompression sickness.
- *Age.* There is an increased incidence of decompression sickness with age: each decade roughly doubles the susceptibility.
- *Obesity.* Fat, having a relatively high nitrogen content, predisposes obese individuals to decompression sickness.
- *Individual susceptibility.* Certain individuals are more susceptible than others in comparable circumstances, and this susceptibility varies from day to day.
- *Subaqua swimming.* Swimming underwater exposes the body to an increased ambient pressure (atmospheric pressure plus the pressure of water, which varies with depth). If air is breathed underwater, nitrogen will enter the body until the partial pressure of nitrogen equals the ambient pressure. Flying, even at low cabin altitudes, after subaqua swimming is very likely to result in decompression sickness. This increased susceptibility lasts for up to 48 hours, and it is recommended that flying should be avoided for at least 12 hours following exposure to a pressure of up to 2 atmospheres absolute (33 feet (10 m) of sea water), as in subaqua swimming, and at least 24 hours when exposure exceeds 2 atmospheres.
- *Hypoxia.* Coexistent hypoxia makes an individual more prone to the symptoms of decompression sickness.
- *Fatigue.*
- *Ill health.*
- *Recent alcohol intake.* This can increase significantly the likelihood of decompression sickness.

Symptoms

The symptoms of decompression sickness may be summarised as follows.

Bends The 'bends' is pain arising in and around certain joints in the limbs. The most common sites are the upper part of the arm near the shoulder, the wrists, the elbow, the knee and the ankle. It may start as a mild ache in one or more of these areas, progressing to a deep severe pain spreading up and down the affected limb. It can eventually give rise to clumsiness, weakness and complete disablement of the limb. Rubbing or moving the limb makes the condition worse. On descent, symptoms usually pass off but will recur immediately on reascent.

Creeps This is a transient, mild, itching or tingling feeling, usually of the thigh and trunk. A blotchy red rash may sometimes accompany the condition. In itself it is not a serious condition, but it indicates the presence of decompression sickness.

Chokes This is a name used to describe respiratory symptoms, which may be preceded by 'bends' pain. It is characterised by a burning feeling in the chest with pain on breathing in, often accompanied by severe bouts of dry coughing. In spite of the name, there is no respiratory obstruction and no danger, therefore, of choking. Although rare, the condition must be treated seriously and descent should be initiated immediately, to avoid serious complications. The individual should receive expert medical care as soon as possible.

Nervous system symptoms Symptoms of decompression sickness arising from the central nervous system are very varied and may take the form of a temporary loss of areas in the visual field, inability to concentrate or weakness and

paralysis of a limb. The last symptom is the origin of the diver's name of 'staggers'.

Decompression collapse This is a serious condition that may be primary, secondary or post-decompression. Primary collapse occurs with little or no warning. There is a feeling of apprehension, pallor of the skin and a cold sweat, which may be followed by a faint. Secondary collapse is similar, but is preceded by some other form of decompression sickness, usually chokes or severe bends. This is the commonest form of collapse. Post-decompression collapse occurs after return to ground level, usually within 4 hours, but it can occur after many hours. It may be preceded by headache, nausea or a feeling of malaise. Decompression collapse is uncommon but, should it occur, it must be treated as a medical emergency.

Treatment

If decompression illness occurs in flight, administer 100% oxygen, land as quickly as possible and seek urgent specialist assistance and immediate transfer to a hyperbaric chamber facility.

Cabin pressurisation

The sections on hypoxia and decompression sickness have shown the need for protection from these hazards. In passenger-carrying aircraft these problems are overcome by pressurising the aircraft cabin.

Environmental requirements of a pressure cabin

The physiological ideal for a pressure cabin would be to pressurise it to sea level, but this would require an extremely strong and consequently very heavy and complex cabin or fuselage structure. This is incompatible with the need to carry a large number of passengers, baggage and freight over long distances. Aircraft are therefore designed with cabin differential pressures that are a compromise between the physiological ideal and the economic realities of the aircraft's role and performance.

In general, pressure cabins fall into two broad categories, low- and high-differential cabins. The advantage of a high cabin differential is that it protects the occupants of the cabin from any serious effects of hypoxia without having to use personal breathing equipment, and there is no risk of decompression sickness at the cabin altitudes maintained (commonly 6,000–8,000 feet [1,800–2,400 m]). Passenger-carrying aircraft normally have high-differential cabins. These aircraft must be able to operate at high altitudes for long periods and they are able to carry the weight of pressurisation equipment that is necessary. A low-differential cabin is usually found in military aircraft in which the crew use personal oxygen equipment routinely. When pressurising aircraft cabins the following factors must be controlled:

- pressure
- relative humidity
- mass flow
- volume flow
- temperature.

If these factors are adequately controlled, the problems of cabin conditioning, i.e. temperature and ventilation, are also taken care of.

In modern passenger aircraft, it is normal for 50% of the cabin air to be recirculated. This recirculated air is passed through high-efficiency particulate filters (HEPA filters), which remove bacteria and viral particles. The benefits of recirculating air are an increase in relative humidity and a reduction in ozone levels, as well as reduction in uncomfortable drafts of fresh air. Flow rates of fresh air in passenger aircraft cabins are designed to exceed the minima laid down for indoor rooms by the American Society of Heating, Refrigeration and Air-conditioning Engineers (ASHRAE). This rate is 5 cubic feet (142 litres) per minute per person, which ensures that carbon dioxide levels remain below 5,000 parts per million by volume. Most modern airliners achieve flow rates of approximately double this value.

Methods of pressurisation

A pressure cabin is built strong enough to withstand its maximum intended pressure differential, plus an element for safety, and is sealed to meet regulatory standards for leak rates. Pressurisation is then achieved by tapping air from a suitable stage of the engine compressor, cooling it and ducting it into the cabin. In some aircraft, a separate engine-driven or electrically driven compressor is used. The differential pressure level is then set by controlling the inflow of compressor air together with a fine control for regulating the rate of escape of air from the cabin by means of a barometrically operated outflow valve. The cabin altitude is usually allowed to increase with aircraft altitude until a cabin altitude of between 5,000 and 8,000 feet (1,500 and 2,000 m) is reached. Barometric control of the outflow valve then maintains the cabin at that altitude until the maximum differential pressure for that aircraft cabin is achieved. If the aircraft continues to climb, the maximum differential bleed valve control takes over, the maximum differential pressure is maintained and the cabin altitude increases, maintaining that differential over ambient atmospheric pressure. In reality, it is rare for a commercial airliner to exceed a cabin

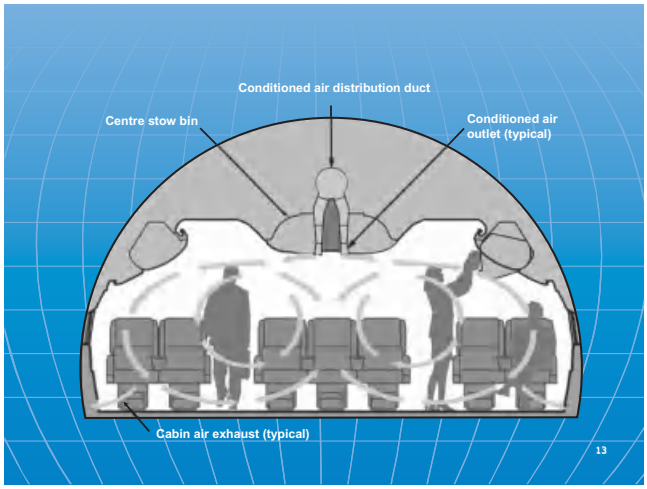

Figure 16.3 Cabin air flow.

altitude of 8,000 feet (2,400 m) during normal operation, with most flights having a cabin altitude of 5,000–6,000 feet.

The air is distributed to the cabin via overhead ducts and grills running the length of the cabin. The airflow circulates around the cabin rather than along the cabin and is continuously extracted through vents at floor level as shown in Figure 16.3.

Loss of cabin pressure

Loss of cabin pressure can vary from a slow leak, due to some minor mechanical problem such as a faulty door seal, to a rapid or even explosive decompression due to a rupture of the cabin wall or loss of one or more windows. The occurrence of a rapid decompression is readily indicated by a loud noise due to the sudden release of pressure. The compressed air within the cabin 'roars' out of the defect at a velocity near the speed of sound until the cabin pressure reaches that of the surrounding atmosphere. As this air leaves the cabin, so the remaining gas expands, causing the temperature of the air within the cabin to drop to its dew-point and water condenses out as a mist, which can be so dense that it interferes with the occupants' vision. The loud noise plus misting has led crews to believe that their aircraft is severely damaged and on fire. In the case of a slow leak, there is no such dramatic indication. The first sign is likely to be the sound of a cabin pressurisation failure warning device, the illumination of the appropriate warning light or a cabin altimeter indication, depending on the aircraft instrumentation.

Possible causes of loss of cabin pressure are:

- compressor failure
- malfunction of the control system
- pressure leakage, especially around doors
- window blowout
- structural failure.

Effects of rapid decompression

The effects of loss of cabin pressure are dependent on:

- the altitude at which the decompression takes place and the presence or absence of aerodynamic suck
- the pressure differential at the time of failure
- the size of the hole permitting loss of pressure and therefore the duration of the decompression
- the volume of the pressurised compartment.

The possible physiological effects, dependent on the factors above, are:

- pressure change effects on ears, sinuses, lungs and gut. Of these, only rapid expansion of trapped gas in the gut is usually of any significance, as in the other sites the expansion is normally counterbalanced by the rate of leakage from the body. Rapid distension of the gut can lead to a faint as a result of vagal inhibition.
- hypoxia, particularly in high-differential cabins where the crew and passengers are not wearing oxygen equipment at the time of decompression
- decompression sickness, if there is any need to continue the flight at cabin altitudes above 25,000 feet (7,600 m)
- cold, depending on the size and position of the defect in the cabin
- difficulty in communication: depending on the size and position of the defect there may be considerable wind noise, which interferes with communication between crew members.

The pressure cabin is an essential part of the modern high-performance aircraft, without which it would not have any useful high-altitude capability. Without pressurisation, air crew and passengers would only be able to carry out high-altitude flying by the continuous use of personal oxygen equipment, which of course would not be acceptable for the transport of fare-paying passengers.

Sleep and fatigue

Sleep is essential for restoring the normal balance between the different parts of the central nervous system. During sleep, the body's physical functions are rested and some renewal takes place; sympathetic nervous activity decreases and the muscular tone becomes almost nil; the arterial blood pressure falls, the pulse rate decreases, the blood vessels in the skin dilate and the overall basal metabolic rate of the body falls by up to 20%. On average, most humans need physiologically about 8 hours of sleep per night; however, in

modern society most adults report an average of 7–7.5 hours sleep per night, with 75% reporting daytime sleepiness [5].

Sleep loss can be acute or cumulative. In an acute situation, sleep loss can occur either totally or as a partial loss. It can accumulate over time into what is referred to as 'sleep debt'. As little as 2 hours of sleep loss can result in impairment of performance and levels of alertness. Sleep loss leads to increased reaction time, reduced vigilance, cognitive slowing, memory problems, time-on-task decrements and optimum response decrements. It has also been shown that performance variability increases with sleep loss.

Physiology of sleep

Sleep can be divided into five stages: stages 1 to 4 and rapid eye movement (REM) sleep. Stage 1 is a transitional phase between waking and sleeping and this normally lasts around 10 minutes as an individual falls asleep. Sleep then becomes deeper, with 15 minutes in stage 2 sleep and a further 15 minutes in stage 3 sleep before moving into stage 4. Approximately 90 minutes after sleep onset, REM sleep will occur. The cycle of REM sleep and stages 1–4 sleep repeats during the course of the night in 90-minute cycles, each succeeding cycle containing greater amounts of REM sleep. An 8-hour sleep period will typically contain about four to five bouts of REM sleep. Most stage 4 sleep happens early in the night. It is thought that stages 1–4 sleep are related to body restoration, whereas REM sleep may be related to strengthening and organising memory. When learning new tasks, an increased proportion of REM sleep is seen.

The need to operate commercial airliners worldwide for 24 hours each day inevitably leads to the problems of unsocial and irregular hours, time zone (transmeridian), climatic and cultural changes, sleep disturbances and alterations to circadian rhythms. Fatigue is the main danger for flight crew, as a decline in performance is likely to accompany it. The economic and operational requirements of an airline must be balanced against these undesirable factors, but good air crew scheduling has been developed to minimise the effects on health, morale and safety.

For passengers travelling by air, the effects of sleep loss and fatigue are likely to be less critical than for air crew. However, when important business decisions have to be taken after a long journey it is essential that the traveller has some understanding of the nature of sleep and fatigue so that the effects of sleep loss and circadian disruption can be minimised.

Scheduling

For flight crew, there are statutory constraints on scheduling. These constraints include limitations on the maximum flying duty period, minimum rest periods, maximum scheduled duty hours and minimum cumulative off duty periods. Airlines operate schedules that are further restricted by the need to meet the needs of passengers and to comply with night flying bans, peak hour saturation and political influences on route planning. In addition, flight time limitations usually reflect conditions acceptable to industrial bodies rather than to medical advisers. The commercial need to keep aircraft flying, and so earning revenue, and the requirements of engineering schedules for airframe and engine inspection and checks are also relevant considerations.

Transmeridian travel

The endogenous circadian system, in which over 50 physiological and psychological rhythms have now been identified, is known to be affected by many environmental factors. These include local clock hour, light and dark, and temperature, although many of the rhythms continue in the absence of such cues, albeit usually with a slightly prolonged periodicity. The environmental factors facilitate entertainment or phasing of the rhythms and are known as synchronisers or 'Zeitgebers' (time givers). Travel across time zones outstrips the ability of synchronisers to entrain rhythms and desynchronisation occurs. This is responsible for the syndrome known as jet lag, as circadian rhythms need a finite period to become re-entrained to local time (usually estimated at about 1 day per time zone crossed). Westward travel is generally considered to be better tolerated than eastward, possibly because the endogenous system, with a natural periodicity in most individuals of about 25 hours, is more able to adapt to the longer 'day' encountered during westward flight.

The aetiology of the effects of jet lag – sleep disturbances, disruption of the other body functions such as feeding and bowel habit, general discomfort and reduced psychomotor efficiency – has been the subject of much investigation. This has largely concentrated on underlying hormonal variations, but for air crew and business travellers the important changes are those associated with performance levels. Ability at many mental skills, including vigilance, choice reaction time and simulator performance, rises to a peak during the day between 12.00 and 21.00, with a dip during the afternoon, and then falls to a minimum between 03.00 and 06.00. Results of memory tests peak in the morning and then fall steadily.

Sleepiness and fatigue

There are two principal components of sleepiness or fatigue:

- physiological sleepiness or fatigue – this is a requirement like hunger or thirst and can only be reversed by sleep

• subjective sleepiness or fatigue – this is an individual's perception of their sleepiness but it may be affected by other factors. It may be difficult for an individual to subjectively assess their own alertness, with a tendency to report a greater level of alertness than is actually the case.

Factors affecting sleepiness include:

• prior sleep and wakefulness
• circadian phase leading to:
  • increased sleepiness in the early hours of the morning and during the afternoon
  • decreased performance in the early hours of the morning
• age (the amount of nocturnal sleep required reduces after the age of 50)
• alcohol (reduces the quality of sleep)
• work and environmental conditions.

Prevention and management of fatigue

Individuals have different needs and react differently to sleep loss. Therefore each individual must apply recommendations to suit their particular circumstances.

Sleep scheduling

• At home the best possible sleep should be obtained before a trip.
• On a trip, as much sleep per 24 hours should be obtained as would be at home.
• Feelings should be trusted: if the individual feels sleepy and circumstances permit, then they should sleep; however, if the individual wakes spontaneously and cannot get back to sleep in about 15–30 minutes, then they should get out of bed.

Good sleep habits

• A regular pre-sleep routine should be developed.
• Sleep time should be kept protected.
• The individual should avoid going to bed hungry, but should not eat or drink heavily before going to bed.
• Alcohol or caffeine should be avoided before bedtime. An optimum dark, quiet and comfortable sleep environment is important. A healthy lifestyle with regular exercise should be maintained, which seems to help with the first stages of sleep. Caffeine consumption may be used to increase alertness. A cup of coffee usually takes about 15–30 minutes to become effective, and the effect lasts for between 3 and 4 hours. A balanced diet, including drinking plenty of fluids, can also prevent the onset of fatigue.

Bright light (more than 2,500 lux), used at the appropriate time in the circadian cycle, can help to reset the circadian clock. After flying east, the traveller should be exposed to evening light with respect to body time, but morning light avoided. Conversely, when travelling west, morning light should be sought and evening light avoided. This makes the best use of the natural Zeitgebers in resetting the body clock.

When used appropriately, certain drugs can help in the short term to resynchronise the sleep cycle after time zone crossing. Temazepam is a short-acting benzodiazepine that is rapidly cleared from the body. Many people find this drug helpful in promoting sleep and, used for 2–3 days after travel, it can assist in resetting the sleep cycle. Melatonin is a substance secreted by the pineal gland with a rhythm linked to the light–dark cycle through the suprachiasmatic nucleus. It is available in tablet form and has been used by many people in an attempt to assist sleep; however, the timing of administration to match the late evening part of the pineal circadian cycle is critical. Also, despite being a natural substance, the long-term side effects are not fully understood, particularly those affecting reproductive function and cardiac activity. It therefore does not have a pharmaceutical licence in many countries for general use, which means no control over origin or purity of the tablet ingredients. Although alcohol is widely used as an aid to sleep, it is a non-selective nervous system depressant and is effectively a drug. Although alcohol may induce sleep, REM sleep is considerably reduced and early waking is likely. It is therefore not appropriate to use alcohol in this manner.

It should be remembered that there is no simple or single solution for combating the effects of sleep loss and jet lag. The individual has to discover what helps them, and evolve the appropriate strategies to suit their particular needs.

Motion sickness

Motion sickness is a condition characterised primarily by nausea, vomiting, pallor and sweating, which occurs when humans are exposed to real or apparent motion stimuli with which they are unfamiliar and hence unadapted. It is a generic term that embraces sea sickness, air sickness, car sickness, swing sickness, simulator sickness, ski sickness, camel sickness, space sickness, etc. – all various forms of the same malady named after the provocative environment or vehicle. Despite the diversity of the causal environment, the essential characteristics of a provocative stimulus and the response of the afflicted individual are common to all these conditions, hence the use of the general term motion sickness. Nevertheless, it must be acknowledged that the term motion sickness is, in certain respects, a misnomer. First, because symptoms characteristic of the condition can be

evoked as much by the absence of expected motion as by the presence of unfamiliar motion, such as in simulator sickness and Cinerama sickness. Second, the word 'sickness' carries the connotation of being affected with disease and tends to obscure the fact that motion sickness is a quite normal response of the healthy individual, without organic or functional disorder, when exposed for sufficient length of time to unfamiliar motion of sufficient severity. Indeed, under severe stimulus conditions, it is the absence rather than the presence of symptoms that is indicative of true pathology, for only those individuals who lack a functional vestibular system are truly immune [6].

Symptoms and signs

Typically, the development of motion sickness follows an orderly sequence, the timescale being determined by the intensity of the stimulus and the susceptibility of the individual. The earliest symptom is usually epigastric discomfort, which is normally described as stomach awareness. Should the provocative motion continue, wellbeing usually deteriorates quite quickly, with the appearance of nausea of increasing severity. At the same time, facial pallor may be observed and the individual begins to sweat, the sweating usually being confined to those areas of skin where thermal sweating rather than emotional sweating occurs. This is followed by the so-called avalanche phenomenon, with increased salivation, feelings of bodily warmth, lightheadedness and, not infrequently, quite severe depression and apathy. By this stage vomiting is usually not far away, although there are some individuals who remain severely nauseated for long periods and do not obtain the transitory relief that many people report following the act of vomiting.

Apart from these characteristic features of motion sickness, other signs and symptoms are frequently, although more variably, reported. In the early stages, increased salivation, eructation and flatulence are commonly associated with the development of nausea, and hyperventilation is frequently observed. Headache is another variable prodromal symptom and complaints of tightness round the forehead or of a buzzing in the head are not uncommon. Another symptom commonly associated with exposure to unfamiliar motion is drowsiness, and, typically, feelings of lethargy and somnolence persist for many hours after withdrawal of the provocative stimulus and nausea has abated. The soporific effect of repeated motion stimulus on infants has long been recognised and it may be that the drowsiness observed in the adult when exposed to appropriate motion is a manifestation of the same mechanism, although this is conjecture.

Incidence

Motion sickness is a normal response to an abnormal environment. Thus, individuals who are unadapted to a particular type of motion are all likely to suffer from the disability if the motion is of sufficient intensity and the period of exposure is sufficiently prolonged. Of course there are wide differences in individual susceptibility, although in severe sea states, sickness rates as high as 99% have been recorded [7]. Nonetheless, in less provocative environments a proportion of the population at risk do not succumb. Although many of the factors that determine individual susceptibility have been identified, and the nature of evocative motions recognised, it is still not yet possible to predict with certainty the incidence of sickness in a given population, even when exposed to a motion stimulus that can be defined. This has caused severe problems with the space programme, where the incidence of sickness is in excess of 50%, despite very careful screening of the astronaut population [8]. Similarly, it has proved difficult to predict susceptibility in applicants for military air crew training and an absence of sea sickness or swing sickness does not confer immunity from air sickness. Conversely, a susceptibility to these stimuli does not imply that an individual will in turn necessarily suffer from air sickness.

Air sickness in passenger transport aircraft is nowadays a relatively rare occurrence, the incidence being of the order of 0.4–1.0% [9]. This is largely due to the fact that large jet transports are able to fly above the turbulent weather and a smooth ride is the norm. The incidence is higher in small light aircraft, particularly among passengers unfamiliar with this form of travel.

Aetiology

An explanation of the causation of motion sickness must include the fact that it can be induced not only by motion in which the individual experiences changing linear and angular accelerations, but also by purely visual stimuli without a changing force environment (as in simulators or Cinerama). Furthermore, it must account for the phenomenon of adaptation to the provocative motion, as well as the sickness that can occur when the individual returns to a normal motion environment after having adapted to an atypical one (an example being land sickness on disembarking after a few days at sea).

Undoubtedly the vestibular apparatus plays a significant role in the condition, because, as has been known for more than half a century, individuals without vestibular function do not get motion sickness. Nonetheless, the theory that motion sickness is due to vestibular overstimulation alone

does not account for the fact that sickness may not be induced at quite strong motion stimuli (for example, vertical oscillation at frequencies above 0.5–1.0 Hz), yet weaker stimuli (for example head movement during turns) are highly provocative. Nor does it account for the visually induced forms of motion sickness or the characteristic adaptive phenomenon [9].

The most satisfactory explanation is still provided by Reason's neural mismatch theory, which views motion sickness not as an isolated vestibular phenomenon but as the response of the body to discordant motion cues [10]. In all the situations where motion sickness is provoked, the information transmitted by the eyes, the vestibular system and other sensory receptors is at variance with the information the individual expects, from past experience, to receive. It is postulated that within the central nervous system there is some form of store or memory and with it a comparator, where signals from the sensory receptors and neural store are correlated. If the signals to the sense organs stimulated by the motion agree with the stored association, there is no mismatch and all is well. However, when the input signals do not agree with the expected (stored) information, then a mismatch signal is generated. This has two effects. One is to modify the store so that a new association of cues is elaborated (the store is rearranged), the other is to initiate the sequence of neurovegetative responses which characterise the motion sickness syndrome. Both these responses depend on the duration and intensity of the mismatch signal. A sustained strong mismatch signal is likely to provoke sickness and concurrently a significant rearrangement of the store. Conversely, a weak mismatch signal, provided it is sustained, can allow rearrangement or adaptation to occur without engendering nausea.

In the human's normal typical environment, usually natural movement on the ground, the inputs from the sensory receptors accord with the expected signals. On transfer to a new or atypical motion environment, such as riding a camel or flying in an aeroplane, the comparator signals differ appreciably from those coming from the visual and/or vestibular receptors because the stored information remains appropriate to the typical conditions. With continued exposure, the contents of the neural store are slowly modified so that the intensity of the mismatch signal decreases as the expected signal comes to agree with the sensory input appropriate to the new atypical environment. Thus there is no longer any mismatch. At this stage, the individual may be considered to have adapted to the atypical motion environment, and the symptoms of motion sickness will disappear.

On return to the normal or typical motion environment a mismatch again occurs and this may provoke symptoms similar to those experienced on initial transfer to the atypical environment. This mismatch arises because the expected signals are still appropriate to the atypical environment. The store has now to be rearranged to make it compatible once again with the sensory input. In general this phase of adaptation proceeds more quickly than the initial adaptation to the atypical environment, because the correlations established by long experience are more easily retrieved than new ones can be acquired. By the same argument, should the individual return to the atypical environment, adaptation is likely to be a more rapid process than on first exposure, because the store can be rearranged with the aid of retained stimulus patterns acquired during previous exposures to the atypical environment. If transfer from one specific motion environment to another is frequent, than a stage is reached where the neural store can be modified quite rapidly, so that the mismatch signal is short-lived or of insufficient strength to engender motion sickness.

Unfortunately, this neural mismatch theory does not explain why motion sickness should take the particular form that it does, nor indeed why motion sickness should occur at all. However, the theory is a unifying concept and provides a basis from which to begin to try and explain it.

Provocative stimulus

The neural mismatch theory implies that there is dissonance between the incoming sensory signals and those expected by the neural store. Basically, two sensory systems are involved: the visual system and the vestibular system. The vestibular system is further divided into the angular acceleration receptor system, which is the ampullary receptors of the semicircular canals, and the linear acceleration or force environment receptor system of the utricular and saccular maculae, usually referred to as the otolith organs. Other mechanoreceptors are also stimulated by the changes in the force environment, but in general they act synergistically with the macula receptors and need not be considered separately. The motion cue mismatch can be specified according to the sensory system involved:

- visual–vestibular mismatch
- canal–otolith mismatch.

These can be further subdivided into type 1 conflict, when both systems concurrently signal contradicting or uncorrelated information, and type 2, when one system signals information in the absence of the expected signal from the other system [9].

Individual susceptibility

There are wide differences between individuals in their susceptibility. It used to be thought that a person who is prone to sickness in one motion environment is also likely to suffer when exposed to other types of provocative motion, but, as

already indicated, experience shows this not to be so. However, susceptibility does appear to be a relatively stable and enduring characteristic of the individual, even though it can be modified by environmental and experimental factors.

Effect of age

Susceptibility changes with age, sickness rarely occurring before the age of 2. In childhood, the incidence of sickness increases markedly to reach a peak at puberty (10–13 years) and thereafter susceptibility declines rapidly between the 12th and 21st years. Motion sickness is not a geriatric problem, being quite rare above the age of 50 years [9]. The mechanism underlying the large changes in age susceptibility is not understood, although it is tempting to ascribe the phenomenon to long-term adaptation. It may also be due to a reduction in general neural sensitivity, which is part of the normal ageing process.

Alcohol

It is known that alcohol induces nystagmus. Positional alcohol nystagmus appears in two phases. The first appears within 30 minutes of alcohol intake and shows nystagmus, with the fast component beating to the right if the subject is in the right lateral position and vice versa. This phase lasts about 3–4 hours and is followed by an intermediate period in which no nystagmus is observed. The second phase begins 5–6 hours after the consumption of alcohol and the direction of movement is reversed, in that the fast component beats to the left when the subject is on the right side. The duration of the second phase and the intensity of both phases are related to the maximal blood alcohol concentration, and hence to the amount of alcohol consumed. This second phase always persists for several hours after all alcohol has disappeared from the blood.

It is thought that when alcohol diffuses from the blood into the endolymph of the semicircular canals it does not become evenly distributed. It is less dense than water and so creates a light spot at the ampulla, because the concentration of blood vessels there means that most of the diffusion occurs in this region. If the canal is then oriented appropriately to gravity, this light spot will tend to rise, causing the fluid to move as it would if the head were turning. This leads to nystagmus. The second phase can be explained as follows. When alcohol starts to diffuse back out of the endolymph, the area around the ampulla becomes free of alcohol fastest and this creates a relatively heavy spot, which in turn causes a reversal of the direction of the nystagmus fast beat. This effect on the endolymph causes an increased vestibular sensitivity and hence the finding of motion sickness in susceptible individuals following minimal alcohol intake.

Receptivity, adaptability and receptivity

Receptivity refers to the way in which the individual processes a stimulus within the nervous system. It is suggested that a person who has high receptivity transduces the sensory stimulus more effectively, and that it evokes a more powerful subjective experience than in a person of low receptivity. Hence, according to the mismatch theory, the receptive has a more intense mismatch signal and is therefore more likely to suffer from motion sickness than the non-receptive when exposed to provocative motion.

Adaptability describes the rate at which the individual adapts to an atypical motion environment or, in more general terms, adjusts to the conditions of sensory rearrangement. Those who adapt slowly suffer more severe symptoms and require a longer period for adjustment to the motion than the fast adaptors. It follows that slow adaptors are more susceptible to motion sickness than the fast adaptors, but this does not mean that slow adapters are also receptives, and it has been shown that these two factors are in fact unrelated.

One factor remains. This is the manner in which adaptation is retained between exposures to the provocative motion. Poor retention of adaptation is illustrated by the flying individual who is troubled by motion sickness when flights are separated by several days, but is symptom-free when able to fly regularly with not more than a few days between flights. The individual with the better retention is not so afflicted, such that, once having adapted to the provocative motion of a particular flight environment, they remain free even when flights are quite spasmodic.

Anxiety and neurotic reactions

Nausea and vomiting are not common symptoms of fear and anxiety, although it is often assumed that anxiety coexisting with provocative motion increases susceptibility to motion sickness. However, there is little firm evidence to support this assumption, although it is important to recognise that neurotic reactions may be manifest by sickness in those environments where motion sickness occurs. In the airborne environment, anxiety does not produce motion sickness, but it can be the prime cause of 'sickness in the air', which is a separate condition often associated with phobic anxiety and may be linked to the hyperventilation syndrome.

Prevention and treatment

As always, prevention is better than cure. Having understood some of the aetiology, it is now fairly obvious that head movements should be reduced to a minimum and discordant visual cues (such as reading during the journey with the

head down) should be minimised. Alcohol should be avoided in the 24 hours prior to flight and during the flight itself, particularly if there is any suggestion that the individual may be susceptible to motion sickness.

Drugs

A number of drugs have been shown to be of value in reducing the incidence of motion sickness, or attenuating symptoms of those suffering from the disability. However, as ever, no pharmacologically active agent is entirely specific and they all have side effects. No drug can prevent the occurrence of motion sickness in every member of a population at risk. Drugs currently available for the treatment of motion sickness include antihistamines, phenothiazines and atropine derivatives. The exact mode of action of many of these drugs is not fully understood, other than a so-called vestibular sedative action.

Receptors for some anti-motion sickness drugs are unevenly distributed in the vestibular nuclei, where they apparently modulate, but do not relay, primary sensory inputs. It is thought that a dynamic balance exists between muscarinic cholinergic-activated brainstem neurons, which initiate motion sickness, and noradrenaline (norepinephrine)-activated brainstem neurons, which act against motion sickness development. The action of dopamine and its function in sensory switching in the basal ganglia is thought to be the most likely mechanism of action.

Hyoscine hydrobromide (available in the UK as Kwells) is still the most effective drug in most of the population and has the advantage of a relatively short duration of action. This is an advantage in aviation, but in the marine world it can be a disadvantage. At sea the favoured drug is cinnarizine (sold in the UK as Stugeron) because it has a long half-life and is effective for a day's sailing. It has calcium antagonistic properties and appears to exert a significant depressant effect on the vestibular nuclei, possibly by antagonising the stimulated influx of calcium ions from the endolymph into the vestibular sensory cells. Unfortunately it can cause drowsiness, due to its antihistaminic activity.

Calcium antagonists are potent blockers of neurotransmitter release in the brain and it has been a chance finding that nifedipine (Adalat) has reduced motion sickness, possibly by antagonising the influx of calcium ions into vestibular cells. However, this finding has failed to be reliably repeated under experimental conditions [11].

Adaptation

The most potent therapeutic measure, at least in the long term, is adaptation to the provocative motion through repeated exposure. This is nature's own cure and is obviously the preferred method of preventing sickness, particularly for aircrew who cannot fly when under the influence of anti-motion sickness drugs.

Since 1966, the Royal Air Force has run a programme for the treatment and desensitisation of military aircrew suffering from motion sickness. The programme involves graduated exposure to provocative motion, both on the ground and in the air. The success rate measured by the number of treated air crew who successfully complete flying training is in excess of 85% [12], and similar desensitisation programmes are now in routine use for military air crew throughout the world.

Passenger health

With an understanding of the basic principles of aviation medicine, it can be seen that flying as a passenger should be no problem for the fit, healthy and mobile individual. But for the passenger with certain pre-existing conditions or developing an acute medical problem in flight, the cabin environment may exacerbate the situation. Modern commercial airliners fly with a cabin altitude of between 4,000 and 8,000 feet (1,200 and 2,400 m) when at cruising altitude, which means a reduction in ambient pressure of the order of 20% compared with sea level and a consequent reduction in blood oxygen saturation of up to about 10%. The cabin air is relatively dry, and the limited room available in the non-premium cabin may be a factor to be considered.

In-flight medical problems can result from the exacerbation of a pre-existing medical condition, or can be an acute event occurring in a previously fit individual. Although the main problems relate to the physiological effects of hypoxia and expansion of trapped gases, it is important to remember that the complex airport environment can be stressful and challenging to the passenger, leading to problems before even getting airborne.

Although passengers with medical needs require medical clearance from the airline, passengers with disabilities do not. However, disabled passengers do need to notify the requirement for special needs, such as wheelchair assistance or assignment of seats with lifting armrests, and this should be done at the time of booking.

Pre-flight assessment and medical clearance

The objectives of medical clearance are to provide advice to passengers and their medical attendants on fitness to fly, and to prevent delays and diversions to the flight as a result of deterioration in the passenger's wellbeing. It depends on self-declaration by the passenger, and on the attending

physician having an awareness of the flight environment and how this might affect the patient's condition. Most major airlines provide services for those passengers requiring extra help, and most have a medical advisor to assess the fitness for travel of those with medical needs [13]. Individual airlines work to their own guidelines, but these are generally based on those published by the Aerospace Medical Association [14] and the British Thoracic Society [15] on fitness for travel. The International Air Transport Association (IATA) publishes a recommended Medical Information Form (MEDIF) for use by member airlines and this can be downloaded from the airline website. The MEDIF should be completed by the passenger's medical attendant and passed to the airline at the time of booking to ensure timely medical clearance.

Medical clearance is required when:

- fitness to travel is in doubt as a result of recent illness, hospitalisation, injury, surgery or instability of an acute or chronic medical condition
- special services are required, e.g. oxygen, stretcher or authority to carry or use accompanying medical equipment such as a ventilator or a nebuliser.

Medical clearance is not required for carriage of an invalid passenger outside these categories, although special needs (such as a wheelchair) must be notified to the airline at the time of booking. Cabin crew members are unable to provide individual special assistance to invalid passengers beyond the provision of normal in-flight service. Passengers who are unable to look after their own personal needs during flight (such as toiletting or feeding) will be asked to travel with an accompanying adult who can assist. It is vital that passengers remember to carry with them any essential medication, and not pack it in the baggage checked in for the hold.

Deterioration on holiday or on a business trip of a previously stable condition, such as asthma, diabetes or epilepsy, or accidental trauma can often give rise to the need for medical clearance for the return journey. A stretcher may be required, together with medical support, and this can incur considerable cost. It is thus important for all travellers to have adequate travel insurance, which includes provision for the use of a specialist repatriation company to provide the necessary medical support where necessary.

Assessment criteria

In determining the passenger's fitness to fly, a basic knowledge of aviation physiology and physics can be applied to the pathology. Any trapped gas will expand in volume by up to 30% during flight, and consideration must be given to the effects of the relative hypoxia encountered at a cabin altitude of 8,000 feet (2,400 m) above mean sea level. The altitude of the destination airport may also need to be taken into account in deciding the fitness of an individual to undertake a particular journey.

Particular evaluation may be necessary for cardiovascular disease (e.g. angina pectoris, congestive heart failure, myocardial infarction), deep venous thrombosis, respiratory disease (e.g. asthma, chronic obstructive airways disease, emphysema), surgical conditions, cerebrovascular accident, epilepsy, psychiatric illness, diabetes and infectious disease.

The passenger's exercise tolerance can provide a useful guide on fitness to fly; if unable to walk a distance greater than about 50 metres without developing dyspnoea, there is a risk that the passenger will be unable to tolerate the relative hypoxia of the pressurised cabin. More specific guidance can be gained from knowledge of the passenger's blood gas levels and haemoglobin value.

Table 16.1 shows the guidelines recommended by one international carrier. This list is not exhaustive, and it should be remembered that individual cases might require individual assessment by the attending physician.

As well as the effect of the condition on the sick passenger, account must be taken of the effect or potential effect on other passengers or crew members. It is obvious that an individual should not fly during the infectious stage of a contagious disease, although any risk of transmission of infection in the cabin is usually confined to those passengers seated near to the infected passenger (the 'index case'). Recirculated cabin air is passed through HEPA filters that remove bacteria and viral particles, reducing the risk of infection via air circulation. Any risk is due to person-to-person droplet spread, as in any situation where people sit in close proximity. The determination of infective periods is defined by the American Public Health Association [16]. Most states have strict rules with respect to infectious passengers entering the country; in the UK, the port health authority has strict disembarkation rules for an aircraft that is carrying a passenger suspected of having an infectious disease.

Considerations of physical disability or immobility

As well as the reduction in ambient pressure and the relative hypoxia, it is important to consider the physical constraints of the passenger cabin. A passenger with a disability must not impede the free egress of the cabin occupants in case of emergency evacuation. There is limited leg space in an economy class seat and a passenger with an above-knee leg plaster or an ankylosed knee or hip may simply not fit in the available space. The long period of immobility in an uncomfortable position must be taken into account, and it is imperative to ensure adequate pain control for the duration of the journey, particularly following surgery or trauma. Even in the premium class cabins with more available leg room, there are limits on space. To avoid impeding emergency egress,

Table 16.1 Guidelines for medical clearance

Category	Do not accept	Remarks
Cardiovascular disorders	Uncomplicated myocardial infarction within 7 days	Myocardial infarction less than 21 days requires MEDIF assessment
	Uncontrolled heart failure	
	Open heart surgery within 10 days	This includes CABG and valve surgery MEDIF assessment required up to 21 days postoperatively Transpositions, ASD/VSD, transplants, etc., will require discussion with airline medical advisor
	Angioplasty: no stenting 3 days with stenting 5 days	
Circulatory disorders ommenced anticoagulation therapy requires assessment oagulation therapy requires assessment	Active thrombophlebitis of lower limbs	
Blood disorders	Hb less than 7.5 g/dl	MEDIF assessment required for Hb less than 10 g/dl
	History of sickling crisis within 10 days	
Respiratory disorders	Pneumothorax which is not fully inflated, or within 14 days after full inflation	
	Major chest surgery within 10 days	MEDIF assessment required up to 21 days post surgery
	If breathless after walking 50 metres on ground, or on continuous oxygen therapy on ground	Consider mobility and all aspects of total journey, interlining, etc.
Gastrointestinal disorders	General surgery within 10 days	Laparoscopic investigation may travel after 24 hour if all gas absorbed. Laparoscopic surgery requires MEDIF up to 10 days
	GI tract bleeding within 24 hours	MEDIF required up to 10 days
CNS disorders	Stroke, including subarachnoid haemorrhage, within 3 days	Consider mobility/oxygenation aspects. MEDIF up to 10 days
	Epileptic fit (grand mal) within 24 hour	Petit mal or minor twitching – common sense prevails
	Brain surgery within 10 days	Cranium must be free from air
ENT disorders	Otitis media and sinusitis	
	Middle-ear surgery within 10 days	
	Tonsillectomy within 1 week	
	Wired jaw, unless escorted and with wire cutters	If fitted with self quick-release wiring may be acceptable without escort
Eye disorders	Penetrating eye injury/intraocular surgery within 1 week	If gas in globe, total absorption necessary – may be up to 6 weeks; specialist check necessary
Psychiatric disorders	Unless escorted, with appropriate medication carried by escort, competent to administer such	MEDIF required. Medical, nursing or highly competent companion/relative escort
Pregnancy	After end of 36th week for single uncomplicated	Passenger advised to carry medical certificate
	After end of 32nd week for multiple uncomplicated	
Neonates	Within 48 hours	Accept after 48 hours if no complications present
Infectious disease	If in infective stage	As defined by American Public Health Association (Benenson 1990)
Terminal illness	Until individual case assessed by airline medical advisor	Individual case assessment
Decompression	Symptomatic cases (bends, staggers, etc.) within 10 days	May need diving or aviation physician advice
Scuba diving	Within 24 hours	
Fractures in plaster	Within 48 hours unless splint bivalved	Extent, site and type of plaster may allow relaxation of guidelines. Exercise caution with fibreglass casts
Burns	Consult airline medical advisor	

immobilised or disabled passengers cannot be seated adjacent to emergency exits, despite the availability of increased leg room at many of these positions. Similarly, a plastered leg cannot be stretched into the aisle because of the conflict with safety regulations. There is limited space in aircraft toilet compartments and, if assistance is necessary, a travelling companion is required.

The complexities of the airport environment should not be underestimated, and must be considered during the assessment of fitness to fly. The formalities of check-in and departure procedures are demanding and can be stressful, and this can be compounded by illness and disability as well as by language difficulties or jet lag. The operational effect of the use of equipment such as wheelchairs, ambulances and stretchers must be taken into account, and the possibility of aircraft delays or diversion to another airport must be considered. It may be necessary to change aircraft and transit between terminals during the course of a long journey, and landside medical facilities will not be available to a transiting passenger. At London's Heathrow Airport, for example, transfer traffic accounts for more than 40% of all passengers.

There is often a long distance between the check-in desk and the boarding gate. Not all flights depart from or arrive to jetties, and it may be necessary to climb up or down stairs and board transfer coaches. It is thus important for the passenger to specify the level of assistance required when booking facilities such as wheelchairs.

Oxygen

In addition to the main gaseous system, all commercial aircraft carry an emergency oxygen supply for use in the event of failure of the pressurisation system or during emergencies such as fire or smoke in the cabin. The passenger supply is delivered via drop-down masks from chemical generators or an emergency reservoir, and the crew supply is from oxygen bottles strategically located within the cabin. This emergency supply has a limited duration. Sufficient first-aid oxygen bottles are carried to allow the delivery of oxygen to a passenger in case of a medical emergency in-flight, but there is insufficient to provide a premeditated supply for a passenger requiring it continuously throughout a journey. If a passenger has a condition requiring continuous ('scheduled') oxygen for a journey, this needs pre-notification to the airline at the time of booking the ticket. Many airlines make a charge to contribute to the cost of its provision.

It is usually not permissible for the passenger to use their own oxygen system in-flight. All equipment used on board must meet regulatory standards; the specification for aviation oxygen is higher than that for normal medical oxygen in terms of permissible water content (to prevent freezing of valves and regulators at high altitude). The supplementary or scheduled oxygen provided for use by the sick passenger may be delivered from gaseous bottles, or it may be delivered on some aircraft by tapping into the ring-main system. Some carriers provide molecular sieve concentrators, although these can be expensive to service and maintain. Those airlines that do provide oxygen usually do so only in-flight; if oxygen is required on the ground, e.g. at an airport of transit, the passenger is probably unfit to fly.

Table 16.2 describes the supplementary (scheduled) oxygen product available from one international carrier.

In-flight medical emergencies

An in-flight medical emergency is defined as a medical occurrence requiring the assistance of the cabin crew. It may or may not involve the use of medical equipment or drugs, and may or may not involve a request for assistance from a medical professional travelling as a passenger on the flight. Thus it can be something as simple as a headache, or a vasovagal episode, or something major such as a myocardial infarction or impending childbirth.

The incidence is comparatively low, although the media impact of an event can be significant. One major international airline has reported 3,022 incidents occurring in

Table 16.2 Supplementary oxygen product of one airline

- Oxygen can be delivered via various systems: cylinders, aircraft portable oxygen units or, on B747–400/B777, therapeutic ring main
- Cylinders can be present at flow rates of 2 or 4 l/min. Ring main 4 or 8 l/min. (A passenger requiring 8 l/min would not generally be considered fit to fly)
- 2 l/min provides approximately 23%; 4 l/min provides approximately 40%
- Cylinders

Dumpy	530 litres	Medium	= 2 l/min lasts 4.24 h
		High	= 4 l/min lasts 2.12 h
Invalid set × 2 cylinders, each 170 litres	340 litres	Medium	= 2 l/min lasts 2.50 h
		High	= 4 l/min lasts 1.25 h
Invalid set × 2 cylinders, each 120 litres	240 litres	Medium	= 2 l/min lasts 2.00 h
		High	= 4 l/min lasts 1.00 h

- Masks

Adult Hudson mask and tubing is supplied. Any alternative mask must be provided by the passenger

Table 16.3 In-flight medical incidents reported in 1 year by a major airline (total 2,522 incidents in 34 million passengers)

Incident type	n	%
Gastrointestinal system	563	22.3
Cardiovascular system	551	21.8
Central nervous system	392	15.5
Musculoskeletal system/skin	337	13.4
Respiratory system	256	10.2
Urogenital system	82	3.3
Metabolic system	64	2.5
Otorhinolaryngology (ENT)	34	1.4
Miscellaneous	243	9.6

Table 16.4 Six most common in-flight medical incidents reported in 1 year by a major airline (total 2,522 incidents in 34 million passengers)

Incident	n	%
Faint	377	14.9
Diarrhoea	291	11.5
Head injury	158	6.3
Vomiting	153	6.1
Collapse	136	5.4
Asthma	124	4.9

something over 34 million passengers carried in 1 year [17]. The breakdown of these incidents into generalised causes is shown in Table 16.3.

The top six in-flight emergency medical conditions reported by the same airline are shown in Table 16.4.

Any acute medical condition occurring during the course of a flight can be alarming for the passenger and crew due to the remoteness of the environment. The cabin crew receive training in advanced first aid and basic life support and the use of the emergency medical equipment carried on board the aircraft. Many airlines give training in excess of the regulatory requirement, particularly when an extended range of medical equipment is carried.

Good Samaritans

Although the crew are trained to handle common medical emergencies, in serious cases they may request assistance from a medical professional travelling as a passenger. Such assisting professionals are referred to as Good Samaritans. Cabin crew members attempt to establish the bona fides of medical professionals offering to assist, but much has to be taken on trust.

The international nature of air travel can lead to complications in terms of professional qualification and certification, specialist knowledge and professional liability. An aircraft in flight is subject to the laws of the state in which it is registered, although when not moving under its own power (i.e. stationary at the airport) it is subject to the local law. In some countries it is a statutory requirement for a medical professional to offer assistance to a sick or injured person (e.g. France), whereas in other states no such law exists (e.g. UK or US). Some countries (e.g. US) have enacted a Good Samaritan law, whereby an assisting professional delivering emergency medical care within the bounds of their competence is not liable for prosecution for negligence. In the UK, the major medical defence insurance companies provide indemnity for their members acting as Good Samaritans. Some airlines provide full indemnity for medical professionals assisting in response to a request from the crew, whereas other airlines take the view that a professional relationship is established between the sick passenger and the Good Samaritan and any liability lies within that relationship. To the end of 2009, there is no record of any successful action for negligence or professional malpractice arising out of a Good Samaritan act on board a commercial airliner.

Recognition by the airline of the assistance given by the Good Samaritan is complicated by the special nature of the relationship between the professional, the patient and the airline. Indemnity, whether provided by the airline or the professional's defence organisation, depends on the fact that a Good Samaritan act is performed. If a professional fee is claimed or offered, the relationship moves away from being that of a Good Samaritan act to one of a professional interaction with an acceptance of clinical responsibility. This implies that the professional is suitably trained, qualified and experienced to diagnose, treat and follow up the particular case, and the Good Samaritan indemnity provision no longer applies.

Airlines are always grateful for assistance willingly offered by medical professionals travelling as passengers, particularly when the costs and inconvenience of an unscheduled diversion are avoided. There is no standard industry response, but the expression of gratitude can vary from a quick word of thanks from the cabin crew to a free first-class ticket sent from the office of the airline chief executive. In practice, most airlines provide an immediate reward, such as a bottle of champagne, followed up with a letter of thanks. As already discussed, for reasons of indemnity it is inappropriate to pay a full professional fee to the Good Samaritan.

Follow-up of the passenger after disembarkation is frequently difficult, because they are no longer in the care of

the airline and becomes the responsibility of the receiving hospital or medical practitioner.

Aircraft medical diversion

Responsibility for the conduct of the flight rests with the aircraft captain, who makes the final decision as to whether or not an immediate unscheduled landing or diversion is required for the wellbeing of a sick passenger. The captain has to take into account operational factors as well as the medical condition of such a passenger. In practice, it is rarely possible to land immediately because, even if a suitable airport is in the immediate vicinity, the aircraft has to descend from cruising altitude, possibly jettison fuel to reduce to landing weight, and then fly the approach procedure to land. Consideration has to be given to the availability of appropriate medical facilities, and in many cases, it is of greater benefit for the sick passenger to continue to the scheduled destination where the advantage of appropriate facilities will outweigh the risks of continuing the flight.

Operational factors to be considered include the suitability of an airport to receive the particular aircraft type. The runway must be of sufficient length and load-bearing capacity, the terminal must be able to accommodate the number of passengers on the flight, and if the crew go out of duty time, there must be sufficient hotel accommodation to allow an overnight stay of crew and passengers. The cost to the airline may be substantial, including the knock-on effects of aircraft and crew unavailability for the next scheduled sector, as well as the direct airport and fuel costs of the diversion. In making the decision whether or not to divert, the captain will take advice from all sources. If a Good Samaritan is assisting, they have an important role to play, perhaps in radio consultation with the airline medical advisor.

Telemedicine

Many airlines use an air-to-ground link that allows the captain and/or the Good Samaritan to confer with the airline medical advisor on the diagnosis, treatment and prognosis for the sick passenger [17]. The airline operations department is also involved in the decision-making process. Some airlines maintain a worldwide database of medical facilities available at or near the major airports; others subscribe to a third-party provider giving access to immediate medical advice and assistance with arranging emergency medical care for the sick passenger at the diversion airport.

The link from the aircraft is made using either high-frequency radio communication (HF) or a satellite communication system (satcom). Satcom is installed in newer long-range aircraft, and is gradually replacing HF as the industry norm for long-range communication. HF utilises the Heavyside-Appleton layer of the upper atmosphere to 'skip' radio waves around the curvature of the globe. This layer moves diurnally and HF propagation is also sensitive to atmospheric conditions. There are areas of the world where HF contact cannot be established, and these vary from day to day or hour by hour. This means that occasionally it is not possible to establish an air-to-ground voice link, or, if it is established, contact can be lost for several minutes. Satcom does not suffer from these limitations and usually provides clear and unbroken communication links.

Digitisation and telephone transmission of physiological parameters is a well-established practice; for example, in the remote highlands and islands of Scotland, a consultant obstetrician in a main hospital is able to monitor the antenatal progress of pregnant patients by the digital transmission of routine tocograms from outlying clinics to the hospital. In many parts of the world, electrcardiogram (ECG) data can be digitised and transmitted via a telephone modem for interpretation by a consultant cardiologist at a specialist centre. An aircraft cabin at 37,000 feet (11,250 m) can be considered a remote location in terms of availability of medical support, and the digital technology used in satcom is similar to that used in modern ground-to-ground communication. The advent of satcom has enabled the development of air-to-ground transmission of physiological parameters to assist in diagnosis. Pulse oximetry and ECG are examples of data that can assist the medical advisor to give appropriate advice to the aircraft captain, although the cost-benefit analysis has to be weighed very carefully.

Aircraft emergency medical equipment

National regulatory authorities stipulate the minimum scale and standard of all equipment to be carried on aircraft operating under their jurisdiction. This includes emergency medical equipment. Although these standards stipulate the minimum requirement, in practice many airlines carry considerably more equipment.

In determining the type and quantity of equipment and drugs to include in the medical kits, the airline must obviously fulfil the statutory requirements laid down by the regulatory authority. The following factors should also be considered.

- *Route structure and stage lengths flown.* Different countries of the world vary in their regulations on what might be imported and exported, particularly in terms of drugs. For example, it is illegal to import morphine derivatives into the US, even if securely locked in a medical kit.
- *Passenger expectations.* Premier class business passengers from the developed world expect a higher standard of care and medical provision than passengers travelling on a relatively inexpensive package holiday flight.

• *Training of cabin crew.* The crew must have a knowledge and understanding of the kit contents, for use by themselves or in assisting a Good Samaritan. They must be proficient in first aid, resuscitation and basic life support.
• *Differences in medical cultures.* Ideally, the kit contents should be familiar to any Good Samaritan irrespective of nationality or training. Some authorities require information and drug names to be given in more than one language.
• *Equipment and drugs appropriate for likely medical emergencies.* It is important to audit the incidence and outcome of in-flight medical emergencies and maintain a review of the kit content. This review should also take account of changes in medical practice.
• *Space and weight.* The medical equipment must be accessible, but securely stowed. Some airlines divide the equipment and drugs between basic first-aid kits, which are readily accessible on the catering trolleys, and a more comprehensive emergency medical kit that is sealed and stowed with other emergency equipment. Space and weight are always at a premium within the cabin, and the medical kits must be as light and compact as possible.
• *Shelf life and replenishment.* A tracking system for each kit must be in place to ensure that contents have not exceeded their designated shelf life. Similarly, after use of a kit, there has to be a procedure for replenishment. In practice, the aircraft can depart if the kit contents meet the statutory minimum, even though drugs or equipment have been used from the non-statutory part of the kit. Many airlines subcontract the tracking and replenishment to a specialist medical supply company.

Resuscitation equipment

Although basic cardiopulmonary resuscitation (CPR) techniques are an essential part of cabin crew training, the outcome of an in-flight cardiac event may be improved if appropriate resuscitation equipment is available. This can range from a simple mouth-to-mouth face guard, to a resuscitation bag, and mask and airway, to an endotracheal tube and laryngoscope, to an automatic advisory external defibrillator (AED). The decision on the scale of equipment to be carried has to take account of the same parameters used in determining the content of the emergency medical kits (see above). In addition, a cost-benefit analysis has to balance the cost of acquisition, maintenance and training against the probability of need and the expectation of the travelling public. Indeed, the decision will often be influenced by commercial considerations as much as medical, as seen in the debate on carriage of AEDs on commercial aircraft.

The European Resuscitation Committee and the American Heart Association endorse the concept of early defibrillation as the standard of care for a cardiac event both in and out of the hospital setting. However, the protocol includes early transfer to an intensive care facility for continuing monitoring and treatment, which is not always possible in the flight environment. Despite this inability to complete the resuscitation chain, it is becoming increasingly common for commercial aircraft to be equipped with AEDs and for the cabin crew to be trained in their use. This is partly driven by public expectation. Experience of those airlines that carry AEDs indicates that there may be benefits to the airline operation as well as to the passenger. Some types of AED have a cardiac monitoring facility, and this can be of benefit in reaching the decision on whether or not to divert. For example, there is no point in initiating a diversion if the monitor shows asystole, or if it confirms that the chest pain is unlikely to be cardiac in origin. Lives have been saved by the use of AEDs on aircraft and diversions have been avoided, so it could be argued that the cost-benefit analysis is weighted in favour of carrying AEDs as part of the aircraft medical equipment. Nonetheless, it is important that unrealistic expectations are not raised. An aircraft cabin is not an intensive care unit and the AED forms only a part of the first-aid and resuscitation equipment.

Traveller's thrombosis (DVT/VTE)

Concern about a possible association between air travel and deep vein thrombosis/venous thromboembolism (DVT/VTE) has been of particular interest in recent years. Long-haul travel is associated with prolonged periods of immobility, a recognised risk factor for DVT first described by Virchow in 1856. However, there have been concerns as to whether there are other factors specific to air travel which further increase the risk.

In the general population, DVT occurs in 1–3 per 1,000 people per year, of which 20% give rise to pulmonary embolism. Increasing age is known to be a strong risk factor, possibly due to decreased mobility and reduced muscular tone.

The pathogenesis of thrombosis still relies on the basic premise of Virchow, who identified circulatory stasis, hypocoagulability and endothelial injury as the risk factors.Risk factors associated with stasis are:
• surgery
• plaster casts
• paralysis
• bed rest
• pregnancy and puerperium.

Factors affecting coagulability are:
• malignancy
• oral contraceptives
• hormone replacement therapy

- pregnancy and puerperium
- abnormalities of coagulation such as:
  - Factor V Leiden
  - prothrombin 20210A
  - protein C deficiency
  - protein S deficiency
  - antithrombin deficiency
  - high levels of factor VIII
  - high levels of factor IX
  - high levels of factor XI.

Factors affecting endothelial injury include:

- sports injuries
- intensive physical exercise
- localised trauma.

Several clinical studies have shown an association between air travel and the risk of DVT, indicating a dose-response relation, with the risk of VTE in travellers increasing with the distance travelled. A recent case-control study showed that all modes of travel increased the risk of venous thrombosis about twofold, with an absolute risk of one thrombosis per 6,000 flights. However, these were mostly asymptomatic [18].

It has been found that combinations of risk factors synergistically increase the risk of thrombosis. In people with Factor V Leiden, the risk of thrombosis after flying was increased by about 14 times and in women using oral contraceptives, the increase was around 20-fold.

It has also been shown that the risk rises with the number of flights taken in a short time-frame as well as with the duration of the flight. Again, the majority of these clots are asymptomatic and disperse naturally.

Thus, even though the overall risk of venous thrombosis after air travel is only moderately increased, clear subgroups can be identified in whom the risk is higher.

The low humidity of the aircraft cabin does not in itself lead to dehydration. Excessive alcohol consumption may cause dehydration, but there is no evidence that this is a significant risk factor leading to DVT.

Two recent studies of reduced oxygen partial pressure with non-hypoxic control groups found no evidence of coagulation [18]. There is no evidence that hypoxia or the hypobaric environment of an aircraft cabin is a significant risk factor for the development of DVT.

Although there is good evidence for the value of aspirin in preventing arterial thromboembolic disease, its role in the prevention of venous thromboembolic disease is much less clear. The side-effect profile is significant, with one patient in 40 taking aspirin developing symptoms of gastric irritation and a significant incidence of gastrointestinal haemorrhage.

There is no evidence to support the use of aspirin in preventing the development of DVT during flight.

The use of compression stockings is often advocated for the prevention of flight-related DVT. However, their use is contraindicated in peripheral vascular disease as they may induce ischaemia, and they may precipitate superficial thrombophlebitis in individuals with varicose veins.

For those travellers at medium to high risk of DVT, there is evidence that stockings appear to substantially lower the risk of asymptomatic DVT, but it remains unclear as to whether this reduction is clinically significant.

One study has shown that for 20–40% of travellers, the commercially available stockings do not fit adequately. It is thus essential for compression stockings to be correctly fitted so as to provide adequate compression to stimulate venous return.

The use of low molecular weight heparin is often advocated for the prevention of DVT. Although its use in the aviation setting is not supported by direct evidence, in a high-risk traveller consideration may be given to a single prophylactic dose prior to flying.

While the relative risk of developing venous thrombosis when flying is significant, the absolute risk of developing symptomatic DVT is very low. The absolute risk of developing a pulmonary embolus during or after a flight between the UK and the east coast of the US has been calculated as less than 1 in a million.

Medical practitioners need to be circumspect in advising any preventive measures, taking careful account of efficacy and risk profile of the preventive method.

Spread of infectious disease

Humans are the primary source of airborne bacteria and viruses and are the most important reservoirs of infectious agents on aircraft. There have been a number of studies in the US and Europe and most microorganisms isolated from occupied spaces, including aircraft cabins, are human in source. They include microorganisms shed from exposed skin and scalp, and from the nose and mouth, which are usually normal human body flora and very rarely cause infections.

Studies have shown no statistically significant differences in concentrations of colonies of microorganisms and fungi:

- among different aircraft, airlines or flight durations
- between aircraft cabins and other types of public transport vehicles
- between aircraft cabins and typical indoor and outdoor urban environments.

Because the prime source of infection is person-to-person droplet contact, the risk of exposure to infectious individuals is highest for the passengers seated closest to a source individual. Microorganisms suspended in cabin air will be removed by the high-efficiency particulate air (HEPA) filters

during the air recirculation process, but these provide no protection from the cough or sneeze emitted by an infected neighbour. However, even without HEPA filters, the progressive and rapid dilution of cabin air and its removal overboard by the environmental control system greatly reduces the concentration of infectious organisms from that found in the immediate vicinity of the infected individual. Fortunately, the natural or acquired immunity of most individuals prevents the development of infectious disease.

Studies of potential infectious disease transmission on aircraft have considered influenza, legionella, measles and tuberculosis (all of which have been suspected of transmission on board aircraft), meningococcal disease and acute respiratory infections, such as the common cold. In fact, the prevalence of transmissible tuberculosis among air travellers is estimated to be 5 to 100 per 100,000 passengers, depending on the route flown. Certainly transmission of acute infectious illness during flight is rarely reported.

Droplet transmission occurs when contagious droplets produced by the infected host are propelled a short distance through coughing or sneezing and come into contact with a susceptible individual's conjunctiva, mouth or nasal mucosa.

Available data indicate that infectious agents can be transmitted from person to person aboard aircraft on the ground and during flight, just as they can in any other situation where people find themselves in close proximity. There is no evidence that the pressurised cabin itself makes transmission of disease any more likely, and it has been shown that recirculation of cabin air is not a risk factor for contracting symptoms of upper respiratory tract infection. Data suggest that risk of disease transmission to other passengers within the aircraft cabin is associated with sitting within two rows of a contagious passenger for a flight time of more than 8 hours.

On the ground once the aircraft doors are closed, air conditioning is provided from the auxiliary power unit until it can be supplied from the aircraft engines, so giving the dilution and filtration benefits of air recirculation.

Newly emerging infectious disease

Severe acute respiratory syndrome (SARS) is an atypical pneumonia caused by a novel coronavirus which first appeared in the Far East in 2003. The outbreak highlighted the potential for air travel to facilitate the spread of infectious disease around the world. The key problem was posed by passengers who were usually asymptomatic but incubating the illness.

Thousands of flights took place to and from WHO-defined 'affected areas' during the outbreak, but transmission occurred only on five flights involving 29 secondary cases (24 cases on one flight). In addition, a further 40 flights were identified on which one or more probable cases (i.e. symptomatic at the time of travel) travelled but where no secondary cases developed. Thus the risk of transmission on board an aircraft is thought to have been low.

Avian influenza ('bird flu') is a highly pathogenic strain A/H5N1 causing an epidemic among birds in Asia, Europe and Africa. It is primarily an animal disease transmitted between poultry by coughs and faeces. Human infection is very rare but serious when it occurs. During 2006, WHO reported a total of 109 cases, of whom 79 died. None of the reported cases occurred within Europe, and air travel is not thought to have been a risk factor.

On the other hand, pandemic influenza has an intermittent occurrence in humans causing major morbidity and mortality, with serious economic and social consequences. Emergence of a new strain of virus in the human population is unpredictable and does not always occur in the winter season. It usually affects a large proportion of the global population due to the absence of immunity, and spreads very rapidly throughout the world. Pandemic influenza has great potential for disruption to travel and international commerce as individuals refuse to travel to certain areas or are too ill to work. Influenza pandemics occurred in 1918 ('Spanish flu'), 1957 ('Asian flu') and in 1968 ('Hong Kong flu'), all with high mortality. During 2009, a pandemic occurred of H1N1 influenza ('swine flu'), although the death rate was lower than predicted by WHO and national public health authorities.

The WHO strategy for rapid containment of an emerging influenza pandemic aims to interrupt disease transmission by isolating and treating infectious individuals, treating and quarantining exposed people, and minimising the exposure of uninfected persons. Modelling suggests that restricting air travel will not prevent the global spread of pandemic influenza, but might delay the spread sufficiently to allow countries time to prepare.

Guidelines are in place for flight crew and management of ill passengers, and can be accessed from the web sites of the World Health Organization [19] and the Centers for Disease Control [20]. It is important that individuals should not travel on commercial aircraft when they have a febrile illness.

Death in flight

Death in flight is a cause of distress to everybody concerned. The number of people who travel on domestic and foreign airlines each year is approximately 1 billion, so the laws of chance suggest that there is a risk that some of those travellers may reach the end of their natural life during the course of a flight. One major airline reported 10 deaths in flight

during a year in which it carried over 34 million passengers [17]. A major aim of pre-flight medical clearance is to reduce the chance of an acute medical event and the risk of death in flight.

Death can legally be confirmed only by a registered medical practitioner. If a doctor is not present on board the aircraft, and in the absence of an AED or monitor, or of the telemetry of an ECG, cabin crew may continue resuscitation attempts until the aircraft lands. Death can then be confirmed by the receiving physician. If a doctor is in attendance on board, or confirmation of asystole is given by an AED or telemetry, the captain is required to record the event, including details of time of death and the geographical coordinates where death occurred. Medical diversion is not appropriate once death has been confirmed, and may only complicate matters for the next of kin.

The regulations for the procedure to be followed on landing vary greatly between countries. Indeed, when landing in certain states police may detain the cabin crew while investigations into the circumstances of the death on board are investigated. This can take several days, or even weeks, and so it may be advisable to avoid the suggestion that the passenger has died during the flight. In the UK, the police must be notified and the event will be reported to the Civil Aviation Authority and to the coroner.

The storage and disposition of the body in the aircraft for the remainder of the flight can cause difficulties. There is inevitable distress for the cabin crew, the accompanying relatives and for fellow passengers. In some cases, it is appropriate to leave the body in the seat covered with a blanket. In other cases, it may be more appropriate to leave the body on the floor of a galley covered with a blanket, particularly if there have been resuscitation attempts. It may not be appropriate to store the body in a toilet compartment, despite the apparent attraction of this option. The cubicle is small, and there may be difficulties in removing the body at the end -of the flight, particularly if rigor mortis has occurred. Each case must be considered individually.

Many airlines have in place a procedure for the follow-up of crew members involved in a distressing event, such as an on-board death. This can be valuable in avoiding long-term post-traumatic stress disorder, and also in reinforcing the training that the crew member has undergone.

Birth in flight

This is a happier event for all concerned, but not without risks to the mother and baby. For this reason, many airlines refuse to carry women in the later stages of pregnancy, typically after the 36th week for a single uncomplicated pregnancy or the 32nd week for a multiple pregnancy. One major airline reports an average of one in-flight birth per year out of a total of more than 34 million passengers carried [17].

Cabin crew receive training in assisting childbirth, and in most countries a delivery pack is a statutory component of the in-flight emergency medical equipment.

Conclusion

The passenger cabin of a commercial airliner is designed to carry the maximum number of passengers in safety and comfort, within the constraints of cost-effectiveness. It is incompatible with providing the facilities of an ambulance, an emergency room, an intensive care unit, a delivery suite or a mortuary. The ease and accessibility of air travel to a population of changing demographics inevitably means that there are those who wish to fly who may not cope with the hostile physical environment of the airport, or the hostile physiological environment of the pressurised passenger cabin. It is important for medical professionals to be aware of the relevant factors, and for unrealistic public expectations to be avoided.

Most airlines have a medical advisor who may be consulted prior to flight to discuss the implications for a particular passenger. Such pre-flight notification can prevent the development of an in-flight medical emergency, which is hazardous to the passenger concerned, inconvenient to fellow passengers and expensive for the airline. For those with disability, but not a medical problem, pre-flight notification of special needs and assistance will reduce the stress of the journey and enhance the standard of service delivered by the airline. The importance of adequate medical insurance cover for all travellers cannot be overemphasised.

Finally, as with all things in commercial aviation, there is a continuing audit of activity and an ongoing risk–benefit analysis. The industry is under constant evolution, and is now truly global in its activity. Application of basic physics and physiology, and an understanding of how this may affect underlying pathology, will minimise the medical risks to the travelling public.

References

1. Bagshaw M (1999) Cosmic radiation measurements in airline service. *Radiat Prot Dosim* **86**(4): 33–33.
2. Hosegood I (2004) Occupational health issues in ultra-long range (ULR) airline operations. Proceedings of IATA Cabin Health Conference. Geneva.
3. Davies DM (1993) Cosmic radiation in Concorde operations and the impact of the new ICRP recommendations on commercial aviation. *Radiat Prot Dosim* **48**: 121–124.

4. Beninson D and Dunster HI (1991) ICRP public statement, London, 9 May 1991.
5. Rosekind MR *et al*. (1994) Alertness management in flight operations. NASA *Technical Memorandum*, DOT/FAA/RD-93/18.
6. Miller AD and Graybiel A (1970) The semicircular canals as a primary etiological factor in motion sickness. In 4th Symposium on the Role of the Vestibular Organs in Space Exploration, SP-187, pp. 69–82. NASA, Washington.
7. Bles W *et al*. (1984) Prediction of seasickness susceptibility. In: Motion Sickness: Mechanisms, Prediction, Prevention and Treatment. Conference Proceedings 372, **27**: 1–6. AGAR D,/NATO, Neuilly sur Seine.
8. Homick JL *et al*. (1984) Space adaptation syndrome: incidence and operational implications for the Space Transportation System programme. In: Motion Sickness: Mechanisms, Prediction, Prevention and Treatment. Conference Proceedings 372, **36**: 1–6. AGARD/NATO, Neuilly sur Seine.
9. Benson AJ and Stott JRR (2006) Motion sickness. In: Rainford DJ and Gradwell DP (eds) *Ernsting's Aviation Medicine*, 4th edn, pp. 459–475. Hodder Arnold, London.
10. Reason JT (1978) Motion sickness adaptation: a neural mismatch model. *J Roy Soc Med* **71**: 819–829.
11. Stott JRR (1990) Personal communication.
12. Bagshaw M and Stott JRR (1985) The desensitisation of chronically motion sick aircrew in the Royal Air Force. *Aviation Space and Environmental Medicine* **56**: 1144–1115.
13. Bagshaw, M. and Byrne, N.J. (1999) La santé des passagers. *Urgence Pratique*, **36**, 37–43.
14. Air Transport Medicine Committee, Aerospace Medical Association (2003) Medical guidelines for air travel. *Aviat Space Envir Med* **74**(II): A1–19.
15. http://www.brit-thoracic.org.uk/guidelines/Air-Travel-Guideline.aspx (accessed 30 July 2012).
16. Benenson AS (ed.) (1990) *Control of Communicable Diseases in Man*. American Public Health Association, Washington, DC.
17. Bagshaw M. (1996) Telemedicine in British Airways. *J Telemed Telecare* **2**: 36–38.
18. Kuipers S *et al*. (2007) The absolute risk of venous thrombosis after air travel: a cohort study. *PLOS Med* **4**(9): 1508–1514.
19. http://www.who.int/en/ (accessed 30 July 2012).
20. http://www.cdc.gov (accessed 30 July 2012).

Further reading

Campbell RD and Bagshaw M (2002) *Human Performance and Limitations in Aviation*, 3rd edn. Blackwell Science, Oxford.

Davis JR *et al*. (eds) (2008) *Fundamentals of Aerospace Medicine*, 4th edn. Lippincott Williams & Wilkins, Philadelphia.

Martin T and Rodenberg HD (1996) *Aeromedical Transportation: A Clinical Guide*. Avebury, London.

McNeill EL (1983) *Airborne Care of the Ill or Injured*. SpringerVerlag, New York.

Rainford DJ and Gradwell DP (eds) (2006) *Ernsting's Aviation Medicine*, 4th edn. Hodder Arnold, London.

Chapter 17 Aviation psychology

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Introduction

Aviation psychology is concerned with the contribution of a wide range of psychological perspectives, methods and skills to enabling safe, efficient and comfortable air travel. The most common areas of research, theory and practice emphasise the role of human factors. The earliest applications of psychology in aviation were probably the experimental studies of human vigilance, system design, person–machine design problems, pilot performance and related human factor problems among air crew carried out during World War II, both in the UK and the US. Air crew flew combat missions under extreme levels of physical and emotional stress and had to be carefully selected and trained to cope with the unique and specific challenges of their job.

There has been a considerable increase in the range of psychological applications since then. This has been driven by the growth in commercial aviation after the war, together with the rapid advances in the speed and distances covered by jet-powered aircraft that have made air travel more accessible and revolutionised transportation and communication. A secondary effect has been on human relationships: air travel has changed how we relate to people because almost any destination in the world can be reached in less than 24 hours. Aviation psychology as a subspecialty within organisational and clinical psychology has expanded as a result to encompass the psychological processes of passengers, airline staff and crew.

Human beings have not evolved naturally to fly and there are countless aspects of our physical and psychological make-up that constitute evolutionary barriers to safe, efficient and comfortable air travel. We remain a species that is best designed and equipped to be self-propelling at a few miles per hour in two dimensions under the conditions of terrestrial gravity [1]. Remarkable achievements in engineering have made air travel both possible and highly accessible within the span of a single lifetime. Various penalties are exacted, however, when evolutionary barriers to motion are exceeded. For passengers, these include motion sickness, jet lag, separation from friends and family, and fear of flying. Airline ground staff have to cope with shift work, anxious or aggressive passengers and commercial pressure from managers. Flight crew encounter large variations in arousal and stress at different stages of flight, and there may be additional problems relating to judgement, decision making, perception and concentration, among others. They are an expensive investment for airlines and are constantly subject to selection and assessment. Air travel often brings us into close contact with strangers, and an understanding of the social psychology of behaviour within groups (among passengers) and teams (among crew) is relevant. The aim of this chapter is to provide an outline of the elements of aviation psychology that may be relevant to the health professional who encounters passengers or crew.

Modern air travel

Air travel has never been so accessible or affordable. Almost a billion people worldwide make at least one plane trip per year. Unfortunately, the dream of flight, nurtured by Leonardo da Vinci, the Wright brothers and others, is sometimes tarnished by stress. Three decades ago, air travel was exciting, attracted a small number of the elite and wealthy passengers, was dangerous, an adventure and enabled people to travel at greater speeds than ever before. Passengers were pampered and obedient. The advent of large commercial carriers in the 1960s and the subsequent effects of industry deregulation and the advent of low-cost carriers in many aviation markets has resulted in a very different experience for the modern airline passenger. While airline advertisements continue to promote a glamorous product, the reality is very different for the majority of passengers. They now face increasingly rigid

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and detail security restrictions, instant media coverage of delays, airport chaos and accidents, and often minimum contact with airline staff. The outcome may be high levels of stress, anxiety and even aggressive behaviour among some passengers.

Stress may begin long before passengers set out for the airport. Making travel arrangements, preparing to leave home and saying 'goodbye' to family, friends or colleagues can increase stress and distress. Frequent air travel may also disrupt relationships. Psychologists have studied relationship dynamics both among air crew and passengers, and examined attachment patterns in 'intermittent spouse' relationships. Attachment behaviour in adults (e.g. avoidance, anxiety) and symptoms of emotional distress (e.g. insomnia, isolation, feeling upset) were found to be affected by relationship status, length and strength, with anxiously attached partners displaying or suffering greater distress [2]. Crowds at airports or the close proximity of fellow travellers on board aircraft, coupled with noise, apprehension about travel, fatigue, hunger, emotional arousal due to separation from a loved one, and language and communication difficulties can test even the most resilient and healthiest travelers.

Most passengers have expectations about travel, and these may be built around punctuality, quality of service, or amenities available at airports or on board aircraft. There are times when these expectations are not met, due to delays or poor levels of service. These may be predictable, but no less annoying as a result. Passengers react differently to stress. Some resort to alcohol ingestion to relieve boredom, anxiety or irritation. Others become militant about what they believe to be their 'rights' and may become insistent or hostile towards ground staff or cabin crew. Still others resort to taking medication to reduce anxiety or induce sleep. Each of these coping strategies may, however, further aggravate the situation and increase stress. Many passengers have a fear of flying and psychological treatment for them is both readily available and effective.

Fear of flying

Air travel has become increasingly affordable and accessible in the past 30 years. A large proportion of the population are, however, anxious, fearful or clinically phobic about flying and cannot fully take advantage of this. Estimates vary, but studies consistently report that 15% or more of the adult population of western Europe and North America consider themselves to be afraid of flying [3, 4]. These figures cover a range of presentations, from the individual who meets the clinical definition of phobia or completely avoids flying to those who will fly when necessary but find it an unpleasant and anxiety-provoking experience. The healthcare professional will often be the first point of contact for fearful flyers who seek help and may encounter the full range of anxiety related to air travel.

A fear of flying may have significant detrimental implications for those affected. A reluctance or refusal to travel by air can put personal relationships under stress and mean that visiting family members is difficult or impossible [4]. It may also be accompanied by a sense of shame or heightened emotional distress when faced with the prospect of air travel, particularly if the fearful flyer is bombarded with statistics that demonstrate how safe flying is [5]. If an individual avoids flying required by their professional role, career options may be significantly limited [6]. A reliance on self-prescribed medication or alcohol to manage anxiety may result in aggressive behaviour or even 'air rage', with potentially severe legal consequences [7]. A fear of flying should not be lightly dismissed by healthcare professionals because of the havoc it can wreak in people's lives and because it may be indicative of a more general anxiety disorder [8].

In its clinical form, fear of flying presents as either a specific phobia of flying or panic disorder with agoraphobia, where air travel is a trigger for anxiety [9]. There are a number of assessment tools available to provide a formal diagnosis based on the clinical descriptions of these anxiety disorders [10]. There are also a number of measures that have been specifically designed to assess fear of flying. The most frequently used in published research are the Flight Anxiety Situations and Flight Anxiety Modality self-report questionnaires [11]. It is, however, important to note that studies of prevalence report that while 20% or more of the populations surveyed report a fear of flying that has a substantial impact on their lives, only approximately 2.5% meet the clinical definition of a specific phobia. For the healthcare professional, the implication is that treatment is appropriate for individuals affected by a fear of flying even when they do not match clinical diagnostic criteria.

The aetiology of fear of flying has its origin in a complex combination of psychological, physiological and social factors that will be unique to each individual. The major physiological factors that contribute to developing a fear of flying are due to the environment of an aircraft cabin where the atmosphere is similar to that at approximately 8,000 feet above sea level. In addition, passengers are effectively required to be stationary in a confined space for sometimes extended periods of time, have a restricted view, and are subjected to unusual and unexplained movements and noises. Motion sickness and disorientation are unpleasant in their own right but may also affect an individual's cognitive ability. Both these effects may contribute to a fear of flying. Although modern passenger aircraft have well-designed systems to maintain adequate oxygen levels, as many as half the

passengers may be slightly hypoxic. The physical symptoms of mild hypoxia are similar to those of anxiety and may be interpreted as such, leading to a fear of flying [12].

Fear of flying may be one aspect of a more general anxiety or mood disorder and it is important to evaluate the possibility of this before considering treatment. Other psychological factors, such as stress, anxiety for reasons not related to air travel or low mood which are present when an individual flies, may become associated with flying and increase vulnerability to developing a fear of flying [5].

Anxiolytic medication has not proven to be effective in the long-term treatment of fear of flying or similar anxiety disorders [13]. It can, however, be an effective short-term solution for fearful flyers who need to travel within a timescale which does not allow for psychological intervention [14]. Medication for motion sickness or nausea may be appropriate for fearful flyers who report these symptoms, as anxiety about feeling ill may be one contributing factor.

Research that evaluates treatment approaches for fear of flying shows that psychological interventions are often highly effective. The majority of fearful flyers report that they experience only low levels of anxiety when faced with the prospect of flying and can confidently fly when required for leisure or business following an appropriate psychological intervention [15]. The most successful interventions will be those that are tailored to an individual's unique anxious response. This and the complex aetiology of fear of flying imply that any clinical psychological intervention must be founded in a comprehensive assessment of the individual's anxious thoughts and behaviours and relevant factors in their social environment. It is crucial to check that a fear of flying is not part of a more general psychological problem and to identify factors such as low mood or general anxiety, which contribute to anxiety about air travel. For this reason, if an individual reports that a fear of flying has a significant impact on their life and particularly if they have not benefited from self-help measures or a group programme, referral to a psychologist with experience in anxiety disorders and ideally fear of flying should be considered.

The most effective treatment approaches for a fear of flying that have been examined in clinical trials are exposure, techniques which focus on anxious thoughts, relaxation, and providing information about flying and/or fear and anxiety. All of these are effective at reducing anxiety and are often used in combination. Exposure, as used in psychological interventions, describes an approach to treatment where the patient encounters the event that triggers fear or anxiety, in this case flying. The rationale is to provide an experience that contradicts expectations of disaster and therefore reduces the tendency of the fearful flyer to associate flying with danger. Exposure is the most effective form of intervention for any anxiety associated with a clearly identified trigger. It is, however, very challenging for the anxious or fearful individual and is associated with high drop-out rates [13]. In practice, it is most often used in a graded form, starting with situations that provoke no more than moderate anxiety, which are practised until that anxiety reduces before moving to a more challenging situation. A fearful flyer might start by driving a friend to the airport, progress to going into the airport with them for a drink or meal and then take a short flight with a sympathetic companion before flying independently. Virtual reality exposure therapy where such experiences are simulated by a computer is an effective option although access may be limited to specialist clinics [15].

Other elements of psychological interventions for fear of flying are most often used to support or enable exposure and are most effective when tailored to the individual. Techniques that target anxious thoughts such as 'If I fly there will be an accident' or 'I'll have a panic attack' may be successful in treating anxiety even without exposure [16]. They are most effective for fearful flyers whose major symptom of anxiety is unrealistically anxious thoughts. Training in relaxation techniques is appropriate for those who report physiological symptoms of fear or employ safety behaviours such as maintaining a tight grip on the armrests while flying. A fear of flying may be effectively reduced by providing information on the flight, aircraft safety or the psychology of fear for individuals who find that information increases their ability to cope, although it should be used with caution, as for some individuals it may actually increase anxiety [17].

A fear of flying that has affected an individual to the extent that they seek help from a healthcare professional is likely to persist without appropriate intervention. Access to specialised psychological treatment is, however, often limited and is unlikely to be funded by public health services or private health insurance. For fearful flyers who are not severely incapacitated by their anxiety, a self-help book that teaches evidence-based techniques may be effective (see for example [18]. There are also a number of airline-sponsored programes that may be a cost-effective approach to reducing anxiety. There are offered as group programmes, normally taking place over one day with lectures on flight safety and relaxation and a specially charted flight where the only passengers are 'students' and staff. Such programmes report that 80% or more of participants are able to fly independently one year after completing the course [19].

Clinical experience, however, indicates that there are a number of reasons why programmes like these may not be suitable or effective for a large proportion of fearful flyers. Those who take part are likely to be those who feel able to join the flight. Those with a deep rooted fear are likely to avoid such courses, so that while the programmes are highly

successful for those who are at least willing to consider taking a flight, they are not suitable for the large proportion of fearful flyers who refuse to fly. A proportion of those who complete group programmes find that the transition from flying with a highly motivated supportive group to travelling independently is too big a step and will need additional support.

In summary, healthcare professionals are increasingly likely to encounter individuals who report a fear of flying with significant negative consequences for their lives. The gold standard for treatment is evidence-based psychological intervention that takes account of an individual's unique combination of social context, psychological state and anxious responses. Medication is a useful short-term solution but is ineffective in the long term.

Passenger behaviour

The quality of the travel experience has significant implications not only for the psychological wellbeing of passengers and crew but also for on-board safety. The increase in accessibility of air travel through cheaper and more frequent flights has meant that there are an ever-increasing number of passengers. The aviation industry has had to invest large resources in maintaining levels of safety while remaining competitive. Aviation psychologists have been at the forefront of initiatives designed to improve safety. These include training in teamwork for multicrew operations (commonly termed 'crew resource management'), helping to develop 'hardware' and systems to reduce error, and improving the design and layout of the aircraft cabin in order to enhance safety. Contributing to an understanding of passenger behaviour has been an important addition to this.

Research into passenger behaviour has, until recently, been overlooked because it was assumed that all passengers are compliant with and adaptive to the unique demands of air travel; however, the increase in the frequency and severity of disruptive passenger incidents, including recent deaths, has challenged this belief. The safety implications of passenger behaviour have thus assumed greater significance and have come to dominate the aviation psychology agenda.

There are a number of factors that impinge on the traveller, each of which may directly or indirectly influence passenger behaviour [20]. These factors include the quality of the travel experience and the traveller's ability to cope with potential stressors during the journey. For those who find managing the travel experience more difficult, lack of effective coping is manifest in behaviours akin to the 'fight or flight' response found in animals. The response is one directed towards either escape or attack in relation to the threatening situation. The lack of 'escape' or avoidance possibilities on board an aircraft has resulted in 'fight' reactions of aggression associated with high anxiety levels. One consequence of this has been an increase in the incidence of threats to flight safety, and in particular to crew and other passengers. While it has always been accepted that a small proportion of passengers who have psychiatric problems may become disruptive on board aircraft, a sense of entitlement, resentment of the authority of crew and stress associated with modern air travel appear to trigger aggression in a wider group of passengers [7, 21].

An air traveller's ability to manage relationships with other passengers is a crucial part of the travel experience, particularly where individual space is compromised. This is especially relevant among air passengers who are likely to come into close contact with people from other cultures. Passengers are required to respond flexibly to the interpersonal dynamics of heterogeneous groups and to manage differences in communication. When passengers have a reduced capacity to cope, due to a lack of skills, knowledge, empathy or high levels of stress, their behaviour can inadvertently exacerbate their own stress. This may lead to anxious and fractious relationships with others. Many passengers resort to using alcohol to cope with boredom and stress. The overuse of alcohol to manage stress has been linked in some cases to so-called 'air rage'.

Passengers' behaviour during flight is directly linked to stress that they experience in their life generally, as well as to the extent of emotional arousal associated with travel and attachment dynamics. Passengers who experience difficulties at work, in their relationships or with their physical health may be more prone to stress when flying and potentially more emotionally charged or aggressive. Frequent flyers are not necessarily immune from stress and results from surveys of business travellers suggest a direct relationship between severity of stress and frequency of trips abroad.

In flight, the traveller has to contend with a number of stressors that may determine how they manage the journey. Beginning with queues for checking-in, to long walks to the departure lounge and air bridge, the traveller has to negotiate crowds, which may be particularly difficult for those unfamiliar with the 'terrain' of large modern airports. Once on board the aircraft, the passenger may feel the need to compete for the armrest or overhead locker space. Airline passengers also have to contend with a physical environment that differs significantly from that experienced in other forms of travel. The lowered air pressure in the cabin is associated with mild hypoxia that results in a reduction in cognitive performance [22]. The air in the cabin is 'recycled' during the flight and mixed with the outside air, which also results in lower humidity [23], and this can lead to an increase in the stress

and irritability of passengers, especially for those on long-haul flights.

The layout of the cabin and seating can also add to levels of stress. The increased seating density in economy class results in a greater propensity for 'crowd behaviour', such as deindividuation, where passengers may become more disinhibited, believing their actions to be 'anonymous' within a group. The physical effects of being in cramped seating for extended periods can lead to health problems, such as deep vein thrombosis, commonly referred to as 'economy class syndrome'. Environmental conditions associated with noise and vibration add to the stress and may lead to irritability.

Flight crew work under the same environmental conditions and they are also affected by the unique conditions aboard the aircraft. The stress this places on crew may impact on passengers and simple customer relations incidents may lead to increased conflict between passengers and crew. The strained relationship between passengers and crew has been suggested as contributing to the increase incidence of 'air rage' [7]. Fatigue and sleep deprivation are additional factors that may affect personal wellbeing and crew–passenger relations.

Passenger safety

An understanding of passenger behaviour is important in relation to flight safety and survivability of air accidents. As a result of improved safety measures that have been implemented over the years, the number of air accidents has decreased. However, this has not been accompanied by a corresponding decrease in the number of passengers who survive accidents or incidents [24]. The actions of passengers on flights where an accident takes place is a crucial factor in determining the degree to which they are injured and the number of fatalities that occur. This is pertinent given the fact that 90% of passengers survive the initial impact in an accident where death is not inevitable [24] and the majority of the fatalities occur in the post-impact period. The number of fatalities at this point is explained four main factors:

- the physical features of the aircraft
- the level of competence of the crew and rescue services
- the environmental conditions both inside and outside the aircraft
- the behaviour of individual passengers and the group.

The likelihood that a passenger will live in a survivable accident is largely determined by their behaviour in the post-impact period. The passenger's response to the accident situation can include one or a number of behaviours. The most usual of these is fear, particularly pre-impact and in the post-impact period where the conditions pose a threat to life. This is commonly accompanied by anxiety associated with identifying and implementing the best strategy to maintain life. These physiological reactions can lead to a variety of behaviours that can either maximise or minimise the passenger's chance of survival. Behaviours that interfere with the passenger's ability effectively to manage the post-impact situation include disorientation, depersonalisation, panic, behavioural inaction and affiliate behaviour, that of searching out familiar objects or people.

Interaction between the air crew and the passengers can be crucial in guiding passenger behaviour to maximise the opportunity for survival in the event of an accident. Cabin crew must inspire the confidence of passengers with respect to their safety. This may have a negative consequence, in that passengers may abdicate responsibility for their own safety to the crew, which may in turn encourage behavioural inaction. In addition, during an accident the relationship between the cabin crew and passengers changes dramatically. Cabin crew must quickly take charge of the passengers to guide them to safety, rather than being at their service. This sudden shift in roles can be confusing for both passengers and crew.

The impact of crew behaviour on air safety has been strongest in the flight deck. As safety measures on the aircraft systems have become progressively more complex, the cause of air accidents has been increasingly attributed to pilot error. Approximately two-thirds of all air accidents are considered to be caused by 'pilot error'. 'Pilot error' is defined as errors that occur due to a failure in the flight deck to manage the flight resources appropriately, but does not include errors associated with the improper use of the controls.

Crew behaviour can be strongly determined by the culture of the flight deck, which is often highly structured and hierarchical. For example, subordinate crew members are reluctant to challenge the captain about a decision. The impact of this culture can be exacerbated by the fact that there are a small number of individuals who are required to execute a large number of complex tasks. In this environment, group processes that take place can mean that individual personalities can play a pivotal role in the overall performance.

Research suggests that most air accidents that are attributed to 'pilot error' result from a breakdown in crew coordination, where crews who make a large number of errors are characterised by having a lower quality of communication, interaction and integration. The quality of communication is of particular relevance and crews who regularly share flight status information, as well as confirm information given, were found to make the least errors. However, crews who made a large number of performance errors tended to communicate in a way that was ambiguous, irritable, uncomfortable or involved a high degree of disagreement among the crew members [25].

Flight crew behaviour has been addressed by airlines through the implementation of cockpit resource management training, including developing effective communication procedures, and through the restructuring of tasks to ensure that the crew work together for these to be carried out. Aviation psychologists play an important role in air crew training by facilitating the improvement of interactions on the flight deck, as well as between the flight deck and the cabin crew.

Jet lag

Universal Coordinated Time (or UTC) is a global time standard in which the world is divided into 24 time zones. Time is determined by the distance from the Greenwich meridian, which passes through London and is the reference point for the system. Fifteen degrees travel in either direction from this imaginary line will change the time by one hour, with travel to the east adding an hour and travel to the west losing one. When a person crosses over a number of time zones, the body's normal 'circadian' rhythm or 'biological clock' is disrupted. The symptoms of this disruption are collectively known as jet lag. The body clock controls when you are sleepy and alert, as well as your hunger, digestion, bowel habits, urine production, body temperature and hormone secretion. This internal timekeeper is normally synchronised with your local time so that one feels hungry in the morning and sleepy in the evening. Two of the most important functions of the body clock are in regulating sleep, and altering mood and mental performance.

With their own internal clock set to local time, crossing time zones means that passengers arrive hours ahead of or behind the time they are expecting. Consequently, the body has to adjust to new times of light, darkness and meals, and often to differences in temperature. It has been suggested that adjusting to new time zones is harder when travelling east (e.g. to Japan, Singapore, Thailand, Vietnam, Australia, New Zealand, etc.) because the body finds it more difficult to adjust to a shorter day than to a longer one. This means that it may be easier to delay sleep for a few hours (westward travel) than to force oneself to fall asleep when one is not ready (eastward travel). Adjustment to a new time zone can take anything up to 10 days depending on age, lifestyle issues, pre-existing physical or mental illness, and the number of time zones crossed within a specific period of travel.

Symptoms of jet lag vary from person to person and will depend on the distance travelled and how many time zones are crossed. Common symptoms include:

- disturbed sleep patterns
- lack of concentration
- lack of motivation
- feeling disorientated, clumsy or confused
- decreased mental and physical performance
- lack of energy
- headaches
- irritability
- loss of appetite
- disrupted digestion and bowel habits
- fatigue [26–28].

Strategies to minimise jet lag include efforts to synchronise the traveller's body clock with the time zone of the destination country by adjusting their sleeping, eating and socialising habits. Travellers should be encouraged to adjust routines to the new time zone before the trip, which may include eating early or going to bed later for a few days before the journey. For trips where the arrival time is early morning, strategies to induce sleep are especially important and include creating the right conditions by reducing noise and light, relaxation techniques and, if necessary, short-term medication. Travellers can also use short 'naps' to gain sleep but the length of these should depend on the duration of the visit to the destination country, as naps of longer than 4 hours can 'reset' the 'internal clock' to local time. Alternatively, air travellers who arrive in the daytime may use different strategies to make themselves more alert, which may include brief exercise or a high-protein meal to boost energy levels.

It is known that bright light (more than 2,500 lux), used at the appropriate time in the circadian cycle, can help to reset the circadian clock. Melatonin is a naturally occurring hormone secreted by the pineal gland that plays a major part in regulating sleep patterns, with a rhythm linked to the light/dark cycle through the suprachiasmatic nucleus. Its release is suppressed when the brain's photoreceptive system is illuminated with short-wavelength light; there is evidence that the system involves the pineal gland and not the retina. This leads to plasma and cerebrospinal fluid concentrations up to 10 times higher at night than in the daytime, although melatonin levels decline with age.

Many studies have been carried out to investigate the efficacy of melatonin as a chronobiotic agent for the alleviation of jet lag symptoms. Herxheimer and Petrie performed a Cochrane review and showed that melatonin is effective in reducing jet lag when used on an occasional basis [29]. The review showed that in 9 out of 10 trials, melatonin taken close to the target bedtime at destination decreased jet lag in flights crossing five or more time zones, with the optimum dose being 5 mg. Reports of side effects were low, except in patients with epilepsy or those taking warfarin.

Melatonin has become a popular remedy for jet lag among those who frequently take long-haul flights, particularly between North America and Europe. It is not available in the UK, but synthetic melatonin can be purchased easily in

North America. The UK regulator for aircrew, the Civil Aviation Authority [30], points out that American-sourced melatonin is not regulated and some products contain little or no hormone and may be derived from bovine products with attendant health risks. They do suggest that it may be useful taken close to the desired onset of sleep if an individual has crossed more than five time zones, but also point out that there is little evidence on the long-term safety of using such products [30]. In a recent review of fatigue management strategies for air crew, it was suggested that melatonin is likely to be useful in assisting adjustment to rapid time zone changes, acting as a soporific and assisting the adjustment of circadian rhythms. It is, however, not useful for promoting sleep during an individual's 'night', and dosage and timing is a complex judgement for those with frequent time zone changes, such as air crew [31]

It is important to note that melatonin is not licensed as a drug in many countries and as routine pharmaceutical control quality has not been established, only pure biosynthetic melatonin should be considered for human use. It should also be noted that melatonin does have diverse physiological actions in humans, which are incompletely understood.

Temazepam is a short-acting benzodiazepine with a short half-life in the European formulation. Many people find a small dose of this drug helpful in promoting sleep and if used for two or three days after travel, it can assist in resetting the sleep cycle.

After flying east, the traveller should be exposed to evening light, but morning light avoided. Conversely, when travelling west, morning light should be sought and evening light avoided. This makes the best use of the natural Zeitgebers (time givers) in resetting the body clock. There is no simple or single solution for combating the effects of jet lag. The individual has to evolve the strategies to suit their particular needs.

Impact of travel on relationships

The negative effects of travelling on the non-travelling partner and family members also have a significant impact on the level of stress experienced by the passenger. Air travellers should be encouraged to develop strategies for managing their relationships with those close to them, particularly relating to explicit communication regarding the trip and the effect it has for all parties. Passengers should also be encouraged to be creative about using the trip as a way to enhance their relationships, such as providing opportunities to express feelings and to explore individual goals of family members. Strategies for managing stress in relationships also include placing the trip in the context of family life by ensuring sufficient warning is given and the reason for the journey is clear [32].

Passengers who have been abroad for extended periods may find returning home a stressful experience and as demanding as arriving in any new unfamiliar environment, a phenomenon referred to as 'reverse culture shock'. Homesickness can also lead to emotional arousal. This may be characterised by obsessional thoughts about home and negative thoughts about the new environment, accompanied by low mood. Travellers should acknowledge their nostalgia and develop skills to ensure that they achieve appropriate social support. They should, however, endeavour to create involvement with and a degree of commitment to the new environment, and should engage in physical activity. Travellers should ensure that they develop an awareness of high-risk situations that are likely to evoke feelings of homesickness [33]. Similarly, travellers who return from long periods abroad often feel a longing for the country they have left, causing significant levels of stress. Travellers experiencing 're-entry shock' often benefit from those strategies applicable to homesickness and should address adjustment reactions.

Stress associated with travel may produce negative consequences socially, psychologically and physically; these can often depend on the individual's ability to buffer stress. Passengers can improve their capacity to manage stress associated with their journey by adopting a proactive stance. Travellers can increase the level of control they have within a threatening situation by either maximising their coping strategies or improving the quality of the existing strategies. The first stage of improving coping, and reducing stress, is for the traveller to identify, in as much detail as possible, those specific parts of the flight that evoke fear. This allows interventions to be appropriately targeted and 'threats' to be distinguished from one another, which is particularly useful given the complex nature of flight phobias. Air travellers should be helped to identify those strategies that are already used and to determine how effective they are at dealing with the stress associated with the situation. They should also be encouraged to develop new coping strategies between journeys and to put these into practice during the next trip. New strategies should be evaluated with the view of improving their effectiveness.

Crew mental health

Psychological problems within the crew population are an insidious threat to safety because of impairments to task performance. Much like aviation itself, mental health as a field or specialty keeps evolving. It has long been accepted that definitions of psychological illness are culturally relative

and have also shifted over time [34]. Aviation mental health is concerned with selecting out those who are unfit to fly; monitoring the psychological wellbeing of those being trained or employed; assessing and treating those who encounter psychological problems; determining how long a person is unfit to fly due to psychological causes or symptoms; and preventing mental health problems through proactive health promotion.

Air crew are in many ways a unique occupational group. They have no office, work shifts and are required to undertake multiple duties at 35,000 feet. It has been suggested that people who fly for a living may have health concerns above and beyond those that work on the ground [27, 35]. Most health concerns specific to the flying profession are thought to be environmental, arising from the unique conditions inside the aircraft. This includes air quality, potable water quality, pressure changes, reduced oxygen in the air at altitude, and exposure to cosmic radiation, vibration and noise. Since most flying jobs entail irregular and frequently changing schedules, long work hours, frequent absence from home and frequent travel across time zones, considerable disruption to biological rhythm can result [28].This can cause sleep problems and fatigue, as well as disruptions to normal patterns of eating and other bodily functions.

Air crew are also required to spend long periods away from partners, family and friends at home. When this is compounded by irregular patterns of work and difficulties with planning ahead, there is a consequential lack of investment in personal living [36]. Whereas some studies demonstrate the importance of relationship support in predicting air crew performance [37, 38], it may equally be that individual competency leads to a happier domestic life. It has been long recognised that stable, happy personal and social relationships can reduce the effect of stress in the workplace, while disruption to personal relationships may exacerbate stress leading to impaired performance at work and mental health risks [39, 40].

Early identification of disruptive social and health threats can help crew to deal with any issues arising before they affect their psychological wellbeing. One thing is to identify stress-related problems, but a far more significant matter is to confront the underlying cause of the problem itself. This is especially true for aircrew as time limitations and long absences from home may complicate an individual's ability to manage their personal lives [36]. Furthermore, air crew work requirements (e.g. prolonged absence from home, sleep deprivation, lack of social support, etc.) can also interfere with their ability to deal with significant life transitions that are thought to occur in the everyday population at large (e.g. bereavement, relationship discord, physical health concerns).

There is little doubt that emotional and physical health issues may arise in crew, often against a background of fatigue and sleep disturbances. The unique work requirements present a number of specific challenges that can exact a toll on individual crew members and demand resilience and unique coping behaviours. The subspecialty of aviation mental health should not be seen to be limited to the diagnosis and treatment of psychiatric and psychological problems. A topic of this scope should also be concerned with the active prevention of psychological disturbance through proactive communication, research and further developments both within the aviation industry and the mental health field.

Air rage

Air rage became the subject of increasing public attention after the terrorist attacks of September 2001. The term describes incidents of violence, threatening or abusive behaviour on board aircraft. Healthcare professionals may encounter anxious travellers who ask questions about the possibility of experiencing air rage or be asked for advice on how to behave when travelling.

Media reports of air rage generally highlight the few instances of physical violence or threatening behaviour that result in legal action or a flight having to divert to land somewhere en route to its intended destination. These incidents may be the trigger for questions from anxious passengers. The airline industry monitors these serious events and disruptive behaviour by passengers – typically smoking in toilets or refusing to comply with crew instructions. An analysis of data from 1999 to 2003 reported that UK airlines carried an average of 106 million passengers annually and recorded an average of 1,080 incidents per year of which 56 (19%) were described as serious, eight resulted in diversion and six returned to disembark disruptive passengers before departing [41]. For the anxious traveller asking for information, the answer is that it is possible that they might encounter such an incident, it is, however, unlikely.

The psychological factors that may contribute to air rage are the increasing discrepancy between advertised glamour and the reality of air travel and the increasing stress of air travel, often associated with airport check-in and security procedures [7]. Aggressive behaviour may also be fuelled by alcohol, which is easily accessible in airports and often on board [42]. The best advice to offer travellers is to plan ahead, for example allowing time for security procedures and ordering special meals in advance, and ensure that their expectations are realistic. It is also sensible to use alcohol in moderation and to pay attention to information or requests from airport staff and crew.

Aviation security

While aviation security measures have been part and parcel of airport life since the 1960s, there is little doubt that the tragic events of 11 September 2001 were a defining point in terms of both necessary counter-measures and passenger threat perception.

The airport security checkpoint as we know it, with its archway metal detectors and cabin baggage X-ray machines, has changed little over the past 40 years. The technologies originally selected for deployment were chosen due to their capability, in the hands of trained operators, to identify dense metallic items, such as guns, grenades and knives – the weapons of choice of hijackers.

The X-ray examination of hold baggage was only rolled out internationally in the late 1980s and early 1990s; the catalyst was the Air India bombing of 1985, yet it was the destruction of Pan Am 103 over Lockerbie in 1988 that saw the global aviation community resolve to ensure the 100% screening of all hold baggage on international flights. However, no longer was the industry solely focusing on metallic weapons carried by hijackers; the detection of improvised explosive devices (bombs in common parlance) was now the objective. As a result, the original monochrome images generated by early X-ray systems were replaced by colour images that aided screeners to differentiate between organic and non-organic materials.

The suicidal attacks on the United States on 11 September 2001, quickly followed on 22 December 2001 by the so-called 'shoe bomber' incident, in which Richard Reid tried to detonate a device concealed in his shoes, demonstrated the fallibility of an aviation security system based exclusively on prohibited item detection in easily accessed areas. The weapons used by the 9/11 terrorists could all be legitimately taken through security checkpoints, and the limitations of archway metal detectors, especially in the screening of shoes, were widely known. By 2002, shoe screening and the ban on a host of pre-9/11 acceptable 'sharps' (sharp objects) became global standards. The net results for passengers in many of the world's busier airports were longer queues, earlier check-in times and, often, delayed flights. This naturally made air travel for many a less than pleasurable experience, increasing passenger stress levels.

Archway metal detectors can only detect metal. They cannot detect explosives, liquids, glass, carbon, wood or ceramic. In effect, there are a wide range of threat items that can be carried on the person through airport security checkpoints. However, it is seemingly perceived by the general public to be an absolute necessity. On occasions when regulators have tried out new systems (millimetre wave imaging solutions and through-body X-ray), passengers have complained if they are not also subjected to screening by metal detectors. It is perceived as being effective and, it would seem, despite its limitations it provides passengers with a level of reassurance. One hopes that it also serves as a deterrent to those with criminal intent.

The August 2006 liquid explosive plot resulted in the authorities further limiting what passengers could take on to aircraft and increased the queues at security checkpoints in doing so. However, while passengers could see the need for security checks, many of the recently adopted policies and procedures appeared to lack reason, resulting in many clashes between passengers and security staff at checkpoints. Typical concerns, to name but two, were the confiscation of duty free products (alcohol and perfumes) bought at one airport when transferring at another airport down route and mothers being asked to taste their own breast milk that had been expressed for infant consumption.

The checks that are in place at airports are designed to prevent any act of unlawful interference with civil aviation. Such acts include hijackings and acts of sabotage not only by terrorists, but also by criminals, asylum seekers and those with mental health issues. The system is also supposed to identify passengers who may pose a threat to a given flight without their being aware that they are a threat – from the duped passenger who unwittingly carries an explosive device onto a plane through to the normally law-abiding citizen who simply becomes disruptive in-flight.

It is important to stress these objectives as many people, within the industry as well as the travelling public, perceive aviation security as being an extension of a counter-terrorist operation. The result of this misconception is something I call 'September 11 Syndrome', whereby the mistaken perception is that all future threats will be carried out by suicidal Islamic fundamentalists, trained as pilots and armed with box cutters. While the threat of Islamic fundamentalism cannot be under-estimated, the associated paranoia has resulted in many passengers and crew unfairly focusing on those passengers who fit the terrorist stereotype – predominantly young, Asian males.

Passenger profiling, as a security solution, is often misinterpreted as being racially driven. However, granted the right training, it is an invaluable tool in our arsenal to counter all threats to aviation – from the intoxicated ladette on a hen weekend through to the most ardent terrorist – as it focuses on the norms of behaviour for a given airline, operating a given route, on a given day at a certain time of the year. The advantage of profiling over the use of existing technologies is that the technologies focus on identifying a suspect item, while profiling identifies intent and, as such, a potentially dangerous passenger who may or may not be armed.

Customs and immigration authorities do not treat all passengers the same and, on a daily basis, they identify people

carrying out illegal acts after they have disembarked aircraft. Yet, despite the obvious advantage of using this approach before passengers enplane, civil libertarian groups object to different passengers being screened in different ways. Regulators, too, have a problem in accepting it as a solution. As it is a subjective process and based on that sixth sense (gut feeling) and an analysis of micro-expressions that cannot be replayed, it is extremely difficult to draft the associated procedures and guidelines and nigh on impossible to test on a daily basis for effectivity; it is far easier to slip a gun into a bag and see whether the X-ray operator can identify the gun on the monitor.

The word 'profiling' is part of the problem inasmuch as it is associated with the Israeli approach to passenger screening and the often lengthy passenger interviews that passengers departing Tel Aviv (and those flying El Al or Arkia to Israel) are subjected to. The essence of profiling (or, as some are now calling it, Passenger Risk Assessement or Behaviour Pattern Recognition) actually lies in the analysis of the appearance and behaviour of the passenger, rather than in the answers to questions posed. For each flight there is a baseline of expectations – who travels the route, how they are dressed, what time they check in and what behaviours are demonstrated – and questions need only be asked if a passenger deviates from that baseline and/or displays unusual signs of stress. The profiler is simply asking themself the question whether the passenger, if he is dressed like a businessman, is also behaving like a businessman and interacting with the world around him in the way one would expect a businessman to do. Likewise with a family travelling on vacation – if they are heading off on a charter holiday, are they interacting with each other and with airport staff in the way one would expect?

Profiling forces the security staff and, indeed, all airport and airline personnel, to apply common sense to the screening process. An exclusively technology-based process cannot differentiate between passengers travelling in December from London to Reykjavik or from London to Bangkok; they would be treated the same. Yet, the expectations of dress and behaviour on the two flights is very different – Iceland is not a popular winter destination for tourists and business travellers dress up warmly, while Thailand is entering its peak tourist season and the dress code is casual. Aside from the visual clues, there are documentary indicators that can also be examined in the passport and travel itinerary, e.g. the routing or frequency with which the passenger travels. A two-day trip to Budapest may now be the norm for a British couple looking for a city break, yet a two-day visit to Detroit is 'unlikely' to be for tourism. We are looking for the 'unlikely' rather than proof of a crime being committed. The most important factor is the passenger's behaviour, especially their eye contact and body movements; signs of stress are being sought out and, if present, are evaluated to determine whether they are due to the nature of the trip or the general stress of flying. In written form, the profiling process seems as if it takes longer than using scanners; in reality it is achieved in a fraction of the time. Most decisions can be made within a few seconds and certainly far quicker than it takes to extract a laptop from a bag and remove one's shoes, jacket and belt for inspection.

Yet, for all its detractors, and there are many, profiling has been proven to work numerous times in the history of attacks against aviation (TWA, 1985; El Al, 1986; American Airlines, 2001; the Domodedovo bombings, 2004), while X-ray has yet to prove its effectiveness.

Risk-taking behaviour among travellers

Most of this chapter deals with passengers on board aircraft. This short section deviates slightly from this context to consider some of the risks to the traveller in a foreign environment and how these may arise. Behavioural scientists who work in public health settings are concerned with a number of issues, among them disease prevention and treatment compliance. Surveys of travel clinic attendees repeatedly confirm that travellers worry about becoming unwell while abroad, due to eating certain foods or drinking contaminated water. Although the effects of such contamination may be unpleasant, they are rarely life threatening and it is usually possible to reduce the risk of gastrointestinal illness while abroad. Research carried out among returning travellers has demonstrated that, unfortunately, a significant proportion of travellers fail to take the necessary precautions or heed the advice given by experts and are unnecessarily exposed to other, and potentially more serious, medical conditions. This also happens in spite of their knowledge and awareness of the risks. Three common examples are:

- contracting malaria by not taking prophylaxis or completing the full course of treatment
- exposure to sexually transmitted infections, including HIV, through unprotected intercourse with a partner abroad
- sunburn (and the increased risk of skin cancer) after not adequately protecting exposed skin.

Although these are different health problems, the common thread of risk taking among some travellers links them. There are several possible explanations why travellers might take unnecessary risks.

In terms of sexual risks, some people make judgements about the degree of risk to which they believe they will be exposed according to the physical appearance of their partner(s). Healthcare professionals sometimes hear patients returning from abroad state: 'he looked too healthy to be

infected', or 'she was too good looking a type to be ill'. Of course, these beliefs are unreliable because sexual infections can be transmitted irrespective of the age or appearance of the person, who may be infected but free of obvious symptoms. The theory of cognitive dissonance [43] suggests that we are prone to making up explanations to fit with our beliefs rather than objective facts. A further example of this strategy to manage dissonance is the smoker who says that the risk to health of smoking is manageable because only a small proportion of smokers contract cancer.

When people are away from home and their usual routine, different decisions may be reached about the acceptability of certain risks. For example, someone may choose to have a brief extramarital sexual relationship while on a business trip because they believe that it poses no significant threat or risk to the relationship with their regular partner. Similarly, having to take medication to prevent malaria may be equated with ill health. This belief may conflict with the sense of fun and relaxation normally associated with recreation and being on holiday. This may be further exacerbated by some of the unpleasant effects of taking antimalaria prophylaxis. Some travellers may also argue that, as they did not detect any mosquito bites on their body, they could not have contracted malaria, thereby justifying their decision not to take prophylaxis. There are attendant risks to gambling behaviour of this kind.

Prevention of some health problems is often associated with having to give up something enjoyable, exposure to something unpleasant or the inconvenience of having to take measures to prevent exposure to infection. In the case of sexual risk, this may necessitate the use of condoms, while, to prevent malaria, a course of medication may need to be completed for the duration of the period of exposure to infection and for several weeks thereafter. Each of these situations is associated with having to weigh up relative risk and the possibility of the inconvenience of behavioural change.

Healthcare professionals who work with travellers should inform them of the risks and encourage behavioural change where appropriate. Intentions are a reasonable prediction of behaviour. Young, single men travelling abroad with friends are at greatest risk of healthcare problems for two reasons. First, they may intend to take sexual and other risks while abroad. Second, the group may influence the individual and his intentions (for example, to tan responsibly or to take condoms when planning a night out). Cofactors, such as alcohol use, may further influence risk-taking behaviour. Counselling of travellers should therefore include some discussion about how they intend to manage different risks, using a range of possible scenarios, and rehearsal of possible situations, linking these to both beliefs and actions.

Giving advice to the traveller

The role of the healthcare professional is crucial in informing air travellers about the necessary precautions they should take before their flight to manage the stress associated with their journey. The greatest risk to the traveller's health is non-compliance with advice given by the health professional [44]. Compliance can be reduced if the advice given to travellers is incomplete or conflicts with information obtained from other sources.

Compliance with advice is reduced when travellers find the information complex or confusing. Eliciting feedback about the traveller's understanding of the information offered therefore provides an opportunity to clarify and elaborate on advice. The delivery of advice given by healthcare professionals can improve compliance if a number of rules are followed [44].

- Avoid using jargon.
- Ensure that both you and the traveller agree on what advice is required and which aspects are most important.
- Ensure any written information you give is understandable.
- Emphasise the relevance of the advice but be aware that the traveller's anxiety levels may interfere with the ability to retain information.
- Complex information should be made simple and concrete and possibly be introduced over a number of consultations.
- Discuss the risks of non-compliance with the traveller.
- After the trip, try to obtain information about the nature and extent of compliance with health advice. Taking the opportunity to discuss information before the trip and compliance after the trip allows the health professional to assess the degree to which the individual's personal, family or cultural beliefs are compatible with the advice given. This permits the health professional to tailor future travel advice by framing information differently or by using motivational interviewing techniques, such as cost-reward assessments, to improve the traveller's compliance with health advice.

Conclusion

Modern air travel is both complex and stressful and places considerable psychological demands on both passengers and crew. Psychologists have played an important role in improving safety in the airline industry, training flight crew in teamwork and in understanding passenger behaviour. Safe and efficient air travel is a team effort and requires close cooperation between crew, ground staff, operators and passengers. Aviation psychology has contributed an understanding to

what happens to individuals, teams and large groups when confronted with the unique and specific demands of air travel. The increase in stress associated with modern air travel means that this understanding will be in greater demand in the foreseeable future.

References

1. Reason J (1974) *Man in Motion: The Psychology of Travel*. Walker, New York.
2. Fraley R and Shaver P (1998) Airport separations: a naturalistic study of adult attachment. *J Pers Soc Psychol* **75**: 1121–1198.
3. Dean RD and Whitaker KM (1982) Fear of flying: impact on the US air travel industry. *J Travel Res* **21**: 7–17.
4. Waterhouse J *et al*. (2006) Occupational factoire in pilot mental health: sleep loss, jet lag and shift work. In: Bor R and Hubbard T (eds) *Aviation Mental Health*, pp. 69–82. Ashgate, Aldershot.
5. Bor R (2007) Psychological factors in airline passenger and crew behaviour: a clinical overview. *Travel Med Infect Dis* **5**: 207–216.
6. Van Gerwen LJ and Diekstra RF (2000) Fear of flying treatment programs for passengers: an international review. *Aviat Space Environ Med* **71**: 420–427.
7. Bor R (1999) Unruly passenger behaviour and in-flight violence: a psychological perspective. *Travel Med Int* **17**: 5–10.
8. Van Gerwen L (2003) Sociodemographic and clinical characteristics of people who self refer for treatment for their fear of flying. In: Bor R and Van Gerwen L (eds) *Psychological Perpectives on Fear of Flying*, pp. 1–18. Ashgate, Aldershot.
9. Wilhelm FH and Roth WT (1997) Clinical characteristics of flight phobia. *J Anxiety Disord* **11**: 241–261.
10. American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association, Washington DC.
11. Van Gerwen LJ *et al*. (1999) Construction and psychometric characteristics of two self report questionnaires for the assessment of fear of flying. *Psychol Assess* **11**: 146–158.
12. Vanden Bogaerde A and De Raedt R (2008) Cognitive vulnerability in fear of flying: the role of anxiety sensitivity. *Depress Anxiety* **25**: 768–773.
13. Choy Y *et al*. (2007) Treatment of specific phobia in adults. *Clin Psychol Rev* **27**: 266–286.
14. Wilhelm FH and Roth WT (1997) Acute and delayed effects of alprazolam on flight phobics during exposure. *Behav Res Ther* **35**: 831–841.
15. Bor R and Van Gerwen LJ (2003) *Psychological Perspectives on Fear of Flying*, 1st edn. Ashgate, Farnham.
16. Bor R (2003) Brief, solution-focused psychological treatment for fear of flying. In: Bor R and Van Gerwen L (eds) *Psychological Perspectives on Fear of Flying*, pp. 168–185. Ashgate, Aldershot.
17. Verschragen M *et al*. (2003) The effect of information about aviation on fearful flyers. In: Bor R and Van Gerwen L (eds) *Psychological Perspectives on Fear of Flying*, pp. 28–39. Ashgate, Aldershot.
18. Bor R *et al*. (2009) *Overcome Your Fear of Flying*. Sheldon Press, London.
19. Doctor RM *et al*. (1990) Long-term behavioral treatment effects for the fear of flying. *Phobia Pract Res J* **3**: 33–42.
20. Lazarus R and Folkman S (1984) The concept of coping. In: Monat A and Lazarus R (eds) *Stress and Coping*, pp. 189–206. Columbia University Press, New York.
21. Bor R *et al*. (2001) Survey of the world's airlines about managing disruptive passengers. *Int Civil Aviat Org J* **56**: 21–30.
22. Denison D *et al*. (1966) Complex reaction times at simulated cabin altitudes of 5000 feet and 8000 feet. *Aerospace Med* **37**: 1010–1013.
23. Edwards M and Edwards E (1990) *The Aircraft Cabin: Managing the Human Factors*. Gower Technical, Brookfield, VT.
24. Muir H and Marrison C (1989) Human factors in cabin safety. *Aerospace* **4**: 18–22.
25. Foushee H and Manos K (1981) Information transfer within the cockpit: problems in intracockpit communication. In: Billings CE and Cheaney ES (eds) *Information Transfer Problems in the Aviation System*. ASA Report No TP-1875, NTIS No.N81-31162. NASA-Ames Research Center, Moffet Field, CA.
26. Caldwell J (1997) Fatigue in the aviation environment: an overiew of cause and effect as well as recommended counter measures. *Aviat Space Environ Med* **68**: 932–938.
27. Richards P *et al*. (2006) Psycological factors relating to physical health issues: how physical factors in aviation and travel affect psychological functioning. In: Bor R and Hubbard T (eds) *Aviation Mental Health: Psycological Implications for Air Transportation*, pp. 27–39. Ashgate, Aldershot.
28. Waterhouse J *et al*. (2006) Occupational factors in pilot mental health: sleep loss, jetlag and shift work. In: Bor R and Hubbard T (eds) *Aviation Mental Health: Psycological Implications for Air Transportation*, pp. 209–227. Ashgate, Aldershot.
29. Herxheimer A and Petrie KJ (2001) Melatonin for preventing and treating jet-lag. *(Cochrane Review)*. *Cochrane Database Systems Review* (1): CD 001520. Issue (1).
30. Civil Aviation Authority (2004) Medication Alcohol and Flying, Aeronautical Information Circular 99/2004.
31. Caldwell JA *et al*. (2009) Fatigue countermeasures in aviation. *Aviat Space Environ Med* **80**: 29–59.
32. Persaud R (1999) When will I see you again? *Bus Trav* **3**: 50–52.
33. van Tilburg M *et al*. (1996) Homesickness: a review of the literature. *Psychol Med* **26**: 146–158.
34. Bor R and Hubbard T (2006) *Aviation Mental Health*. Ashgate, Aldershot.
35. Brown T *et al*. (2001) *A Consultation on the Possible Effects of Health, Comfort and Safety of Aircraft Cabin Environmenmt*. Institute for Environment and Health, Liecester.
36. Eriksen C (2009) *Managing Work and Relationships at 35,000 Feet*. Karnac, London.
37. Levy DE *et al*. (1984) Work and family interaction: the dual carrer family of the flight attendant. *J Soc Relations* **11**: 67–88.
38. Rigg RC and Cosgrove MP (1994) Aircrew wives and the intermittent husband syndrome. *Aviat Space Environ Med* **65**: 654–660.

39. Dallos R and Draper R (2000) *An Introduction to Family Therapy: Systemic Theory and Practice*. Open Univesrity Press, Milton Keynes.
40. Michie S (2002) Causes and management of stress at work. *Occup Environ Med* **59**: 67–72.
41. Bor R (2003) Trends in disruptive passenger behaviour on board UK registered aircraft: 1999–2003. *Travel Med Infect Dis* **1**: 153–157.
42. Tomaro M (2003) Flight crew involvement in the fear of flying. In: Bor R and Van Gerwen L (eds) *Psychological Perspectives on Fear of Flying*, 1st edn, pp. 211–228. Ashgate, Aldershot.
43. Festinger L (1957) *Theory of Cognitive Dissonance*. Stanford University Press, Stanford, CA.
44. Noble L (1997) Communicatring risks to the traveller. *Travel Med Int* **11**: 111–115.

Chapter 18 Expedition and extreme environmental medicine

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EXPEDITION MEDICINE

The tales of explorers and exploration are filled with accounts of heroism against untold odds in the most inhospitable environments. Explorers would often regale the public with stories of comrades lost to wild animals, bizarre tropical diseases and savage natives. Any medic reading the accounts of Stanley's expedition to the Congo or the Lewis and Clark overland expedition to the Pacific Coast of America can only be morbidly fascinated and appalled by the catastrophes the medic and expedition leaders had to face and overcome. They had limited resources but were hugely capable and ingenious. Their unconventional methods in unconventional conditions should often be a lesson and inspiration to all of us who now rely heavily on our technical diagnostic tools. Fortunately, few of these causes of mortality are encountered on current-day adventures. Some elements of the environments visited have obviously changed, but the main changes are the result of improving medical capabilities and infrastructure.

In the last decade with the advent of adventure and expedition companies, cheap travel and the expansion of the tourist industry worldwide, we are a highly mobile population participating in more and more exciting experiences. We are exposing ourselves to tropical diseases and the vagaries of foreign travel and without the medical infrastructure we accept as the norm in the developed world.

Expedition medicine and the role of the medical officer

What is an expedition? The definition even a decade ago was relatively clear; it was a journey with the purpose of adventure, scientific exploration or community development. Over the past 10 years, however, the advent of commercial and charity adventure travel has blurred the definition somewhat. The leisure industry has created a different adventurer; it has allowed people of all ages and practically any physical condition to participate in foreign adventure. This obviously has implications for the medical support for such trips. The expedition medical officer now has to be competent in treating the accepted conditions associated with adventure travel, and the problems encountered by people with chronic illness in the same environment.

Expeditions by their very nature expose their participants to both hazardous experiences and environments, and medical officers need to anticipate and prepare for these potential dangers.

Our perceptions of potential risks and causes of morbidity and mortality on expedition conjure up images of life-sapping unusual tropical diseases. The reality, however, is quite different. A number of studies over the past 10 years have demonstrated that the overriding common conditions presenting to medical practitioners on expeditions are public health related. Gastroenteritis generates almost 30% of all contacts and hence the importance of ensuring all the expedition team is aware of safe food preparation, water purification and waste disposal. The most important and repeated message from any expedition medic should be 'wash your hands'.

Other common medical conditions depend on the expedition environment: acute mountain sickness at altitude, frostbite in polar regions, dehydration and heat-related illness in the desert, and endemic disease and humidity-related illness in the jungle. Musculoskeletal injuries are particularly common as expeditions tend to be physical environments and the medic must be prepared to manage blisters, tendonitis and the occasional traumatic amputation and fracture.

The most dangerous period of any expedition, whatever the environment, is the transfer to or from the airport. Road

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travel in developing worlds can be treacherous; there may be no or few traffic rules, often no seatbelts and defective vehicles. Ensuring the vehicle appears roadworthy and that the driver is alert and seems competent can reduce the risk of accidents. Animals, though potentially dangerous, are rarely encountered and generally attack only if provoked.

Planning ahead should allow the medical officer to reduce the risks and prepare for the unavoidable accidents with the aim of keeping morbidity to a minimum and eliminating mortality.

Preparation is a crucial element of the role of the expedition medical officer. Many expeditions may not require any medical input while in the field, but it is imperative that the team is equipped for any eventuality. The responsibilities of the medical officer are best divided into three distinct time frames: pre-expedition, during expedition and post expedition.

Pre-expedition

This is possibly the busiest period for the expedition medical officer, making preparations for events in the field. Table 18.1 outlines some of the essential elements of this stage.

Don't underestimate the length of time this pre-expedition phase can take. Some elements are particularly time consuming, especially the medical assessment of the team and creation of an appropriate medical kit, which are universally recognised as a headache.

Also be aware that team members/clients may not be completely honest with their medical history and it is important to try whenever possible to ensure the primary care physician for the client/team member has had some input into the medical screening form. Stress wherever possible that medical conditions not revealed will not be covered by insurance while in the field.

Developing the casevac plan can be made much easier if there has been a previous expedition to the area you will be operating in. Reports can sometimes be found at the Royal Geographical Society (RGS). They can provide a framework for your own casevac and pre-expedition planning. Other useful points of contact include NaTHnac, Travax, CDC, FCO and WHO. The structure of a casevac requires input from as many sources as possible. Contact your insurance company and in conjunction with the medical assistance company explore the various worst case scenarios. Gaps within this structure may need to be filled by local support from medical rescue companies, police and military organisations.

To initiate a casualty evacuation the expedition requires a number of communication platforms. This may be a simple handheld radio system, but it is also worth ensuring the expedition has mobile capabilities or/and satellite communications. In the event of all this failing a personal location beacon (PLB) properly registered is a good final system. Always test the communication system and the casevac plan when you first arrive in country. This can be done by liaising with the insurance company and running a worst case scenario. It highlights any gaps in the system and also increases the awareness of the insurance company about who and where you are.

Table 18.1 Responsibilities of the medical officer in the pre-expedition phase, courtesy of PGMJ review

- Liaise with expedition leader (EL) on selection of team/clients
- Review medical history of team/clients and contact individuals' general practitioner if required (with the permission of the patient)
- Risk assessment of expedition environment, activities and likely diseases
- Initiate creation of Casualty Evacuation (casevac) Plan, assessing expedition and country infrastructure, including transport, communication, insurance, staff, local agents, etc., and liaise with the expedition insurance company and medical assistance company
- Advise team/clients on required immunisations and any malaria prophylaxis
- Provide first aid training where applicable
- Assess medical kit requirements, availability of medications in country and assemble medical kits

During the expedition

This phase commences as soon as the expedition team members begin to assemble. In the very early stages this role should only involve medical cover. Once in field, however, work should begin again in earnest to consolidate the work done in the pre-expedition phase. As the expedition continues, the medical role should be ongoing public health awareness and management, and dealing with any medical problems that arise. Table 18.2 outlines some of the essential elements of the medical officer's role during the expedition.

Expedition or wilderness medicine differs in one major respect from hospital or primary care medicine in the developed world. As the medical officer, you are often alone without the diagnostic tools we have come to rely on. Instead, diagnosis is mainly based on clinical skills. This may result in unnecessary casevacs, but it is much more prudent where possible to err on the side of caution rather than having to deal with increasingly sick individuals in the field: 'If in doubt ship them out'.

Table 18.2 Responsibilities of the medical officer during the expedition, courtesy of PGMJ review

- Reassess medical history of team members/clients if time allows
- (Re)Assess medical kit and restock where needed
- If using a field base, assess camp hygiene, water and food supply, storage and preparation
- Assess infrastructure in field: communications, vehicles, equipment, and make sure all the vehicles have a small medical kit
- Brief team/clients, covering: medical team, medical cover (consultation times), basic camp and personal hygiene, medical issues specific for area operating, first aid training if possible
- Develop, assess and practise casevac plans with the whole team, making contact with in-country support and developing good working relationships
- Treat any medical problems or trauma that arise during the course of the expedition, and in conjunction with the expedition leader assess the ability of expeditioners to continue
- Be available, approachable and maintain the same level of standard of care you would expect at home including confidentiality
- Keep comprehensive medical records

One element of the expedition medical officer's role, which I haven't placed in the table, is medical care of individuals not part of the expedition. This is a contentious area and views differ depending on the expedition team. It is a complex multifaceted area involving perceived wealth, local sensibilities, altered expectations and ultimately perhaps dealing with potential adverse outcomes of treatment. Treating illnesses appropriately and successfully in isolated environments can, however, be a very positive experience for the patient and can build trust between the expedition and the locals. Use your common sense; my own experience and belief is to act in cases of accident and obvious serious illness in children and young adults to the best of your ability, do not be dragged into treating chronic illness or minor illness as news will spread fast and your resources will be stretched. If local guides, agents and porters are away from their normal practitioner they should be treated the same as any other member of the expeditionary team and extended the same medical support.

Post expedition

This phase commences when the expedition arrives home. Table 18.3 outlines some of the essential elements of this stage.

Table 18.3 Responsibilities of the medical officer post expedition, courtesy of PGMJ review

- Provide letter to general practitioner regarding any patients who received treatment, which should be placed in medical records
- Give general advice to team/clients regarding possible symptoms on returning home that should trigger early medical assessment
- Advise that it is essential to continue malaria prophylaxis if appropriate and mention the fact that malaria may not present for up to a year after return (or rarely even longer)
- On longer expeditions, especially involving younger team members, readjustment to home can be difficult (re-entry syndrome). Letters sent to families explaining potential problems can diffuse situations
- If further expedition is expected ensure all equipment is checked and medical kit restocked
- Write a medical report for the expedition

Collating particular medical problems encountered and passing them on can assist further expeditions and aid the Royal Geographical Society Expedition Advisory Centre to support future expeditions in the same region.

Medical kits

Organising the medical equipment for an expedition can be a time-consuming experience. The contents of any medical kit are dependent on a number of factors, not least of these being the medical practitioner's experience and preferences. Further factors include the following.

- Location of the expedition and hence endemic diseases and common medical problems likely to be encountered.
- Proximity to acceptable medical infrastructure (clinics, hospitals, ambulance services, aeromedical services).
- Number of expedition participants.
- Duration of the expedition.
- Nature of expedition (diving, rafting, driving, etc.).
- Number and experience of expedition medical staff.
- Pre-existing medical conditions among the members of the expedition.
- Availability of medicines and equipment within the expedition country.

In all probability more than one medical kit will be required for an expedition, particularly larger expeditions or those active in several different sites. Smaller kits may be given to trekking guides or team leaders. There may be kits in individual vehicles, and of course there will be comprehensive kits carried by the expedition medical officers.

Longer expeditions by their very nature will require larger kits; however, the size of all elements of the kit do not have to be directly proportionate to the length of the expedition. One would expect to require more kit covering the common problems – blisters, sprains, headaches, infections. The same guide can be applied to the size of the expedition party.

Kits being prepared for similar-sized expeditions but in different environments will have to be tailored to problems likely to be encountered in those countries. An expedition going to altitude may wish to take medication to treat altitude-related illnesses, while an expedition to the desert may wish to take more IV fluids, and a jungle expedition would probably wish to have a greater supply of antimalarials and antifungals. Remote expeditions require more comprehensive medical kits, as one is required to be more self-sufficient.

The mode of transport used on an expedition should also be taken into consideration. A desert expedition utilising vehicles will be able to carry a more comprehensive medical kit than an expedition trekking through dense rainforest. If animals are being used to carry kit, the kit can be more inclusive, but always bear in mind the shape of the kit as it may not fit on a yak or in a dog sled.

The kit structure is also dictated by the skills of the expedition medical officer using it. Do not take equipment that you do not know or are unhappy using.

All the members of an expeditionary team should be advised to bring their own personal kit containing basic medication for pain relief and dressings for simple lesions, and obviously any medication that they take at home on a regular basis. It is prudent to advise people with chronic disease to bring double the medication needed and either store half the medication in a safe but accessible place while on expedition, or give it to a member of the medical team. This is particularly important for medication for potentially life-threatening diseases such as cardiovascular disease, diabetes, etc. The following is a rough guide of the essential items for an expedition participant:

- non-narcotic analgesia
- anti-inflammatories
- minor wound care
- personal medications
- zinc oxide tape
- malaria prophylaxis (if in malaria area).

Medical kit, general outline

Individual medics may decide on packing their kit in different ways. A possible overview of the contents of a medical kit is listed below.

- Oral medication (including antibiotics, analgesia, antiemetics, antimotility, etc.)
- IV drugs (analgesia, antibiotics, antipsychotics, antiemetics, etc.)
- ENT
- Ophthalmology
- Topical (creams and powders)
- Wound management and closure
- Orthopaedic (Kendrick and SAM splint)
- Environment (altitude treatment, hypothermia, etc.)
- Primary survey including:
  - Catastrophic haemorrhage control (combat application torniquet [CAT], field dressings and haemostatic gauze)
  - Airway (oropharyngeal [OP[, nasopharyngeal [NP], surgical airway)
  - Breathing (Asherman chest seals)
  - Circulation (intravenous [IV], intraosseus [IO] access, giving sets and fluid)
  - Oxygen if available or EMOX system
- Animal bites (especially in area where snakes, but also to manage dog bites, virucidal agent)
- Dental kit
- Daily treatment and emergency kit (some analgesia, blister treatment, anaphylaxis, asthma, hypoglycaemia, epilepsy)
- Diagnostic (stethoscope, otoscope, ophthalmoscope, BP cuff, urine dip sticks, rapid diagnostic tests [RDTs], beta human chorionic gonadotrophin [BHCG], BM monitor, thermometer, torch, waterproof notebook and pencil, pulse oximeter)

Always remember where possible to have several methods of communication, as medical assistance even over the telephone is often reassuring. Depending on the country, a mobile phone may actually be a vital piece of equipment. Otherwise a satellite phone or suitable radio system will be required.

This only an example and you may well wish to arrange your bags differently.

Maintaining expedition medical kits

Kits need continuous updating, checking the expiry dates and ensuring the equipment remains in good working order. Colour-coding tags can be used to identify drugs that need replacing in a particular year. This is a thankless task.

Any drugs or items used during expedition should be documented, including the date and amount. Not only is it good medical practice but also assists the kit Quarter Master on return.

Travelling with expedition medical kits

Airlines do not allow any sharps on flights unless they are required for chronic disease. It is still prudent to carry a

simple kit containing analgesia, antiemetics and antibiotics. Check current hand luggage guidelines.

There are no restrictions on importing or exporting medical kits from the UK with the exception of controlled drugs (CDs). One can either purchase CDs in the country of expedition, or apply for a Home Office Licence for import and export of CDs from and to the UK. (Though, from the 31 December 2007, an export licence is no longer required for trips of less than 3 months duration). For further information contact www.drugs.gov.uk/drugs-laws/licensing/import-export.

Special permission is also required to import drugs into a country. Requests should be made to the equivalent of the Home Office Drugs Licensing Department of the expedition country. The appropriate department is different for each country and a leaflet containing all the specific departments can be applied for from the UK Home Office Drugs Licensing Agency (4th Floor Fry Building, 2 Marsham Street, London SW1P 4DF; tel 020 7035 0480).

A list of CDs can also be obtained from this department. Unfortunately, ketamine and opiates are both on this list.

IKAR (International Commission of Alpine Rescue) has given significant time and energy to this very issue and has chosen to recommend:

- tramadol injection for sublingual (SL) or IV use (100 mg SL is equivalent to 10 mg morphine)
- morphine and ketamine (at the time of discussion ketamine was not a controlled drug)
- fentanyl, again a controlled drug but available in lozenge/lolly format (Actiq) for buccal administration.

Methoxyflurane is a self-administered liquid inhalation anaesthetic agent used in Australia by retrieval teams and is possibly a drug to watch in the future. There is some debate about its capacity to cause renal toxicity (in huge quantities).

If the medical officer for the expedition is travelling with the party they should have responsibility for the medical kit and carry an official letter on headed notepaper listing all the medication being carried. The medical officer should also carry a form of identification, distinguishing them as a medical officer, doctor, nurse or paramedic. These are simple precautions that can ease the transit through customs and border crossings.

The most dangerous period of any expedition is generally the phase involving transfer to the expedition area. Yet this is the stage at which the medical kit can easily be packed away with the luggage and possibly inaccessible. It is important for a medical officer, if not all medical officers, to be carrying their medical kits, and if more than one vehicle is being used, for the medical team to be spread among the vehicles.

Medical training for remote environments

Expedition and wilderness medicine is in the fledgling phase of developing into an exciting and stimulating specialty. There are a number of medical career paths that allow the medical practitioner to develop some of the skills that are valuable in a remote setting. Traditionally medics have tended to come from general practice or emergency medicine. Any experience in pre-hospital care is an advantage, as is an understanding of the endemic diseases that the medic may encounter, hence the involvement of respiratory physicians in altitude medicine and vascular surgeons in polar medicine. Knowledge not only of the common diseases one may encounter but also an ability to function in a hostile environment is essential.

If as a medic providing support to an expedition you feel you don't have these skills then some training prior to departure is useful. This can either be done among the medics providing support for a trip or there are a number of organisations providing specific training for medics wishing to work in remote or hostile environments. Some of these are even designed for specific environments.

Managing medical emergencies in remote environments

There are some obvious limitations of the ability of the expedition medic to respond to life-threatening emergencies in the field. There is the personal and environmental isolation. You don't have the capacity to call on a colleague for advice or to order some investigations. Hence prior planning and understanding of the life-threatening endemic diseases, fauna and flora is imperative. It is also important to limit risky behaviour as much as the expedition allows, as it will be you picking up the pieces. You need to keep your medical kit or at least your primary survey and medical emergency kit close to hand at all times so you can respond to emergencies quickly. Finally, it is essential you have a robust communication platform to initiate a casualty evacuation if required and also to contact individuals at home for advice. Create a list of contacts that you can use in the event of a difficult condition or life-threatening emergency.

There are few truly time-critical medical emergencies in individuals without pre-existing conditions; however, you need to be prepared for them. The commonest on expedition is trauma. The new primary survey algorithm CABC recognises the limitations of fluid resuscitation and focuses on stopping blood loss at an early stage. Envenomation, though rare, is a potentially life-threatening emergency and should

be treated with haste and rapid evacuation as the effects of envenomation are variable in individuals. Should an expedition carry antivenom is a common question and depends on a number of factors: the time to definitive care, the types of envenomating creatures in the area, ability to keep the antivenom stable (it is a protein and hence may denature), and always balance this against the common allergic response to antivenom and the volume required. The most common time-critical, life-threatening medical condition is anaphylaxis. In a remote environment the time to definitive care can be hours or sometimes days and having enough medical supplies to manage this conditions and prolonged evacuation is imperative. Hence larger volumes of adrenaline and steroids than anticipated may be required and airway management during a prolonged difficult evacuation may require a surgical airway.

Dealing with death on an expedition

Managing the demise of any member of a team or party is always going to be a difficult undertaking. The medic and expedition leader need to manage the rest of the group in a sympathetic manner and to conform with the legal requirements of the country in which the person died. In the event of a death, the expedition leader should attempt to separate the group from any ongoing attempt to resuscitate the casualty. Keeping the group informed is imperative. It is also important to stress the need for a no phone policy. The family of the bereaved do not wish to hear of the death of a loved one through the media or a stranger.

Once the medic has declared the casualty dead on scene there are a number of legal requirements. The death is likely to be classified as death by unnatural causes and hence the police will have to be involved. After contacting the police it is prudent to then contact the relevant embassy, high commission or consulate. They can guide the team through the police process, post mortem, registering the death and ensuring the remains are suitably interned. Estimate that this process may take anything from 7 to 14 days, depending on the country. A number of documents will be required to transport the remains: a death certificate, embalming certificate, no objection certificates from various government ministries and a sealing of the coffin certificate undertaken in the presence of an embassy official from the country receiving the body.

International assistance companies act as intermediaries or facilitators who are the direct representatives of an insurance company. They operate in conjunction with international funeral directors. International funeral directors work alongside insurers and assistance companies as brokers. They deal with all funeral-related matters, complicated paperwork and work with local coroners, magistrates, consulates and other local officials as required, including the police.

Most travel insurance and international private medical insurance (PMI) policies include death under a standard repatriation clause or as an optional extra. The repatriation of mortal remains typically covers body preparation, paperwork, associated certificates, coffin and transportation of the body or ashes of the insured from place of death to home country, and thence to an agreed funeral home. Policies tend to cover reasonable expenses. Most policies have an upper limit of cover, although there are some that offer 100% cover refund. Beware, though, that some policies may not pay out if you die from a pre-existing medical condition. Always check your policy.

Building resilience for individuals and teams – handling the pressure of expeditions

There are a number of pragmatic ways a member of an expedition team, such as the medic, can support the participants through what is likely to be a physically and potentially emotionally challenging experience.

Expedition life can be stressful for physical and emotional reasons.

Physical

- Pushed to physical limits.
- Long periods of time eating and drinking expedition rations, which may be dehydrated or otherwise unusual.
- Periods of dehydration.
- Medium- or long-term exposure to extremes of environment and weather conditions – altitude, cold, heat, etc.
- Time spent in uncomfortable working or living conditions.
- Exposure to hostile or combat conditions.

Emotional

- Expected to live in close proximity to others.
- Experiencing sadness or loneliness due to being a long way from home and loved ones.
- In a new or ambiguous environment.
- Frightened of what is going to happen – personal safety is under threat.
- Frustration related to continuous change of plans or expeditions.
- Disappointment through failure to achieve the goal of the expedition.
- Personality clashes with other expedition members.
- Living and working outside of one's comfort zone.

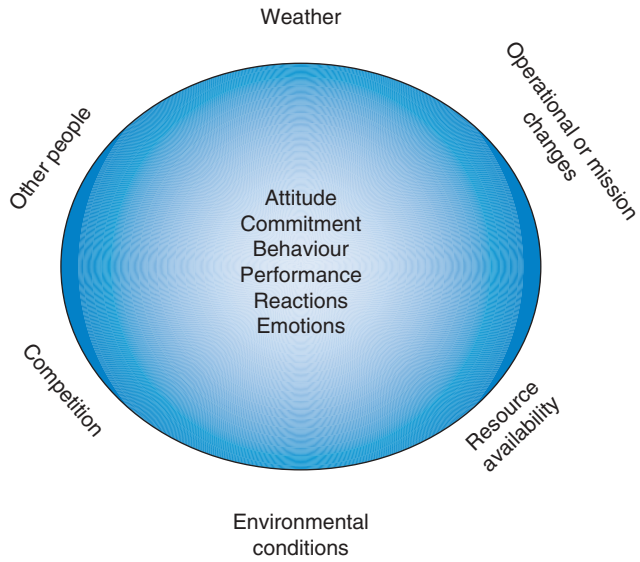

Figure 18.1 Controlling the controllable.

Managing one's own resilience can be challenging enough. As the medic you may be expected to support other expedition members struggling with these challenges.

Individual resilience – handling pressure

Resilience or the ability to operate well under stressful conditions has recently been acknowledged in The Journal of Applied Sports Psychology. Graham Jones created the term 'mental toughness' and based his study on the behaviour and performance of athletes. '*Mental toughness is having the natural or developed psychological edge that enables you to remain determined, focused, confident, and in control under pressure.*' [1]

One specific component of mental toughness is learning how to handle pressure through controlling the controllable (Figure 18.1) and creating coping strategies.

Controlling the controllable

Outside the shaded circle is a selection of factors that may influence how we are feeling but about which we can do nothing. Inside the circle are the factors we can influence and which are worth our attention.

Action point – Control the controllable

- Write a list of or discuss all the things that are preoccupying you – concerns, worries, etc.
- Divide the list into the things you can do something about and the things out of your control.
- Focus your attention on the items within your control.

Creating a coping strategy

Our response to stress and pressure tends to go through a similar cycle each time.

- **Stage 1: Stimulus** – stressful events occur.
- **Stage 2: Response** – mental, physical and behavioural responses.

Problems occur because stage 2 is not a coping strategy. It is often not well thought through and may include inappropriate or undesirable responses.

An effective coping strategy inserts a stage between stages 1 and 2 thus creating a three-stage process.

- **Stage 1: Stimulus** – stressful events occur (e.g. all items in Figure 18.1).
- **Stage 2: Control emotions and organise information**.
- **Stage 3: Response** – mental, physical and behavioural responses.

The ability to control our emotions is influenced by two factors.

- **Factor 1:** Our predisposition to experience or interpret certain events as stressful. For example, one expedition member may find a light aircraft flight into a remote mountain airstrip a terrifying experience while another is unconcerned by this event. As a result one will experience more stress responses than the other.
- **Factor 2:** We need to do an intellectual appraisal of the actual or perceived threat/stress.

Once we understand factors 1 and 2, i.e. that we all have different predispositions to interpret events as stressful and that we need to do a conscious appraisal of stressful events, we can control our emotions, organise the information available, construct a plan and begin to deliver or execute that plan.

So by developing this three-stage process as a coping strategy, stage 3 has clearly thought through and more desirable responses – be they mental, physical or behavioural.

Another useful tip is 'reframing'. This is where we reframe our view or perspective of an event or set of events. Michael Johnson, Olympic Champion, sums this up well.

> We've been trained to think of pressure as the enemy, the unfair burden that holds us down. We see pressure as a compilation of the awful and the impossible . . . It took me some time to realise it, but I love pressure. If there is one thing that will really take you to another level of performance, it might be the ability to embrace pressure, to understand it, to draw it in, to make it your own, and to use it to your advantage . . . Pressure is nothing more than the shadow of great opportunity.
>
> Michael Johnson

Action point – Controlling emotions

Dealing with our emotional response is the key to success. We are not disturbed by events, but the view we take of them. If we can take a third-party position and look in on the situation at ourselves and notice our feelings, emotions and thoughts, we are beginning to become aware of how to deal with them.

- Reframing pressure as a positive energy force and not a negative burden is a powerful technique when it comes to managing pressure. People can be helped to do this with discussion. See the quote from Michael Johnson.
- Encourage trusting relationships where people feel free to discuss their concerns, anxieties and feelings, and help them to process and deal more constructively with the emotions.
- Organise information. Most pressure situations include a volume of information that we feel is overwhelming. By taking the time to organise that information, to sit down, discuss and prioritise, we begin to reduce the pressure and release the stress valve.

Agreeing and knowing one's purpose can help to mitigate other confusing concerns and allow participants to understand *why* they are there. An expedition team with clear and agreed goals and the roles necessary to achieve them will have greater resilience to deal with the physical and mental challenges.

Successful expeditions can be measured in terms of performance goals such as reaching destinations, carrying out the required research or summiting desired mountains. Achieving performance goals is more likely if the team members operate in a way that recognises individual differences and creates a group that is more than merely a cluster of individuals in the same place doing the similar things. Rather, they create a team environment that is stronger and more effective for being together in a group.

We can look at the findings from Katzenbach & Smith's well-respected book, *The Wisdom of Teams*, for a good working definition of a high performance team:

> A small number of people with complementary skills, committed to a common purpose, performance goals and ways of working together for which they hold themselves mutually accountable [2].

These conditions do not normally happen by accident and require work and commitment. It is not simply enough to be told these things by an expedition leader; team members must be included and involved in the discussions that lead to these conditions being met.

Action point – Clarity of goals and roles

- Spend time with the expedition team stating the objective of the expedition.
- Ask team members to state their desired outcomes from being part of the expedition.
- Expedition objectives and personal outcomes should be as complementary as possible. Where personal outcomes do not contribute to achieving the overall expedition objective you must spend time resolving this.

It may be useful to use an impartial facilitator for this process.

Conclusion

Expeditions can be stressful and challenging situations. There are many examples of groups failing to achieve their intended goals due to interpersonal or team dynamic pressure as opposed to technical, medical or equipment failure.

The action points of

- controlling the controllable
- creating a coping strategy
- agreeing goals and roles

should all contribute towards a successful expedition.

ALTITUDE MEDICINE

While high- and extreme-altitude visitation was historically limited to small numbers of experienced climbers, increasing numbers of travellers are choosing high-altitude destinations for their recreation. On the popular Everest trek in Nepal, numbers of trekkers nearly doubled from 2002 to 2008 [3]. Millions visit high-altitude ski resorts every year, many arriving by air, some jetting from sea level to above 3,000 m in just hours, allowing little time for acclimatisation.

Altitude illness can effect up to 40% of visitors to high-altitude ski resorts and vacation destinations [4–6], and that illness can range from mild annoyance to deadly high-altitude pulmonary or cerebral oedema. Despite accessibility of preventive education about safe altitude travel, public and even healthcare provider misperceptions of risks continue to cause preventable altitude illness and deaths, and there is still work to be done. The vast majority of cases of serious altitude illness are preventable when the patient and counsellor are armed with accurate information.

Healthcare providers providing counsel to expeditions and to their patients considering travel to high-altitude

destinations should be aware of the risks inherent in altitude travel so that they may coach their patients and clients on prevention of illness, recognition of symptoms and self-care. Patients with certain pre-existing conditions should be dissuaded from altitude travel, while some may require optimisation and in some cases medication to prevent disastrous outcomes.

Altitude physiology

High altitude (1,500–3,500 m/ 5,000–12,000 ft)

At high altitude, we see the onset of the physiologic effects of lower atmospheric oxygen pressure resulting in decreased exercise performance and increased respiratory rate (lower CO_2) Minor deficits in oxygen transport can be seen on pulse oximetry, but readings should still remain above 90% in otherwise healthy individuals. Because this altitude is common among mountain resorts, large numbers of people routinely ascend rapidly and high-altitude illness is common in this range.

Very high hltitude (3,500–5,500 m/ 12,000–18,000 ft)

At very high altitude, arterial oxygen saturation may fall below 90 and extreme hypoxemia may occur during exercise and sleep. Visitors to very high altitude who have underlying pulmonary disease can be severely affected. Serious and deadly altitude illnesses occur most prevalently in this range, both because of the altitude and the absolute number of travellers in this range.

Extreme altitude (above 5,500 m/18,000 ft)

At extreme altitude, hypoxaemia is so severe that any exertion is difficult. The body's attempts to continue acclimatisation are eventually eclipsed by catabolism and deterioration, which explains why there are no permanent human dwellings at this altitude. Rapid ascents to extreme altitude by unacclimatised individuals without supplementary oxygen are usually followed by severe altitude illness and, in some cases, death.

As altitude increases, barometric pressure falls, as does the partial pressure of oxygen (see Figure 18.2). Although the concentration of oxygen at high altitude remains 21% as at sea level (760 mmHg), the reduced barometric pressure (for example, at 12,000 ft, 483 mmHg) causes hypoxia because roughly 40% fewer oxygen molecules are available per breath.

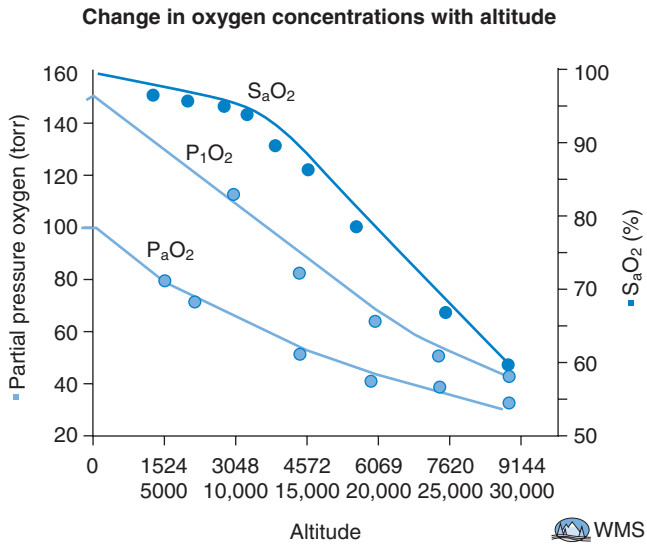

Figure 18.2 Change in oxygen concentrations with altitude. Courtesy of WMS educational powerpoint series. ©www.wms.org

In addition, the relationship of barometric pressure to altitude changes with latitude; as one draws closer to the north or south poles, even less barometric pressure causes less available oxygen to be available at similar altitudes.

Acclimatisation

Sudden exposure to extreme altitudes in the absence of supplemental oxygen (such as in loss of airline cabin pressure at above 8,000 m) results in loss of consciousness and death shortly thereafter. Yet Everest climbers are able to reach similar altitudes slowly over a period of weeks and live to tell the tale. Acclimatisation is the process by which the body's physiology adjusts to hypoxia, allowing not only increased delivery, but more efficient cellular oxygen utilisation.

The ability to acclimatise varies from person to person and from species to species; some adjust quickly without discomfort, while others develop altitude illness and recover or, rarely, never adjust despite gradual ascent. Genetic factors are important to the ability to acclimatise, confounding more than a few elite athletes who incorrectly presume their fitness will supersede their DNA. But even the most genetically advanced altitude dweller can succumb if the rate of ascent is too brisk. Some species of animals have demonstrated the capacity to adapt and thrive at altitude, among them deer mice, llamas, yaks and bar headed geese.

The process of acclimatisation involves a number of changes that allow the body to operate in a hypoxic environment.

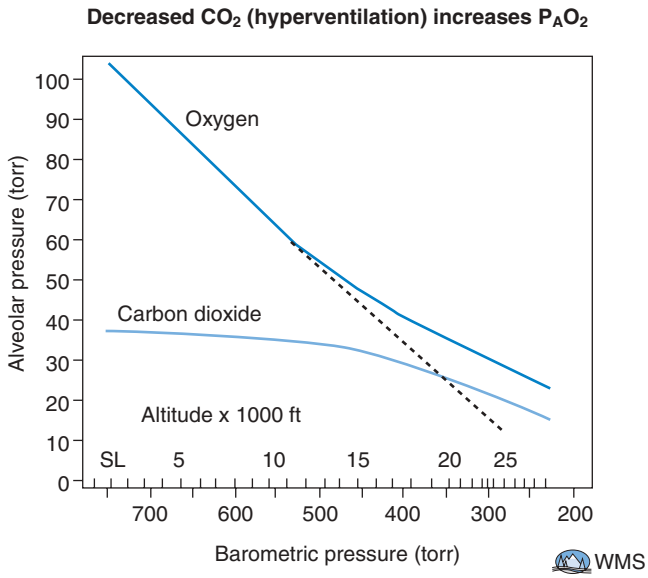

Figure 18.3 Changes in respiration with altitude. Courtesy of WMS educational powerpoint series. ©www.wms.org

• The rate and depth of respiration increases (*see* Figure 18.3); this is affected by the hypoxic ventilatory response (HVR.) The resulting alkalosis is buffered by increased renal excretion of bicarbonate.
• The heart rate increases, and at extreme altitudes, when the limit of acclimatisation is reached, maximum heart rate and resting heart rate converge.
• Cardiac output increases. There is a mild elevation in blood pressure.
• Increased erythropoietin results in increased red blood cell production.
• Increased production of 2,3-DPG causes left-shifting of the oxygen-dissociation curve, facilitating the release of oxygen from haemoglobin to cells.

Depending on the length of time spent at altitude and more importantly individual aptitude, acclimatization may be maintained for a week to in some cases months following descent to low altitude and reascent to the same altitude [7, 8].

Altitude illness

Altitude illnesses are caused by hypobaric hypoxia, and are classified as acute mountain sickness (AMS), high-altitude cerebral oedema (HACE), and high-altitude pulmonary oedema (HAPE). As discussed below, AMS and HACE probably represent different ends of a severity spectrum, and share a common pathophysiology. High-altitude retinal haemorrhage (HARH) and other high-altitude syndromes are discussed, and although the chronic manifestations of altitude on indigenous populations cause substantial health problems and deserve special notice, this discussion is not within the scope of this text.

Acute mountain sickness (AMS) and high-altitude cerebral oedema (HACE)

Definition

Acute mountain sickness (AMS) and high-altitude cerebral oedema (HACE) are clinical diagnoses defined by a collection of non-specific symptoms occurring in the context of a recent increment in altitude. Clinically and physiologically they are considered to represent a spectrum of severity of cerebral oedema beginning with the high-altitude headache of mild oedema, progressing through the more significant oedema of acute mountain sickness to full blown high-altitude cerebral oedema (Table 18.4). A suggestion to differentiate on the grounds of severity as benign or malignant mountain sickness (AMS and HACE respectively), although not widely adopted, does emphasise the potentially fatal consequences of HACE [9]. Those whose physiology has

Table 18.4 Lake Louise Self-report AMS Score [20], courtesy of PGMJ review

1 Headache	0 No headache
	1 Mild headache
	2 Moderate headache
	3 Severe headache, incapacitating
2 Gastrointestinal symptoms	0 No gastrointestinal symptoms
	1 Poor appetite or nausea
	2 Moderate nausea or vomiting
	3 Severe nausea and vomiting, incapacitating
3 Fatigue and/or weakness	0 Not tired or weak
	1 Mild fatigue/weakness
	2 Moderate fatigue/weakness
	3 Severe fatigue/weakness, incapacitating
4 Dizziness / lightheadedness	0 Not dizzy
	1 Mild dizzy
	2 Moderate dizziness
	3 Severe dizziness, incapacitating
5 Difficulty sleeping	0 Slept as well as usual
	1 Did not sleep as well as usual
	2 Woke many times, poor night's sleep
	3 Could not sleep at all

Add the responses to each self-report question. Provided there has been a recent rise in altitude then:
AMS = headache AND at least 1 other symptom AND a total score of 3 or more.

Table 18.5 Categorisation and progression of AMS to HACE

Category	Mild AMS	Moderate – severe AMS	HACE
Symptoms	Headache + 1 or more other symptoms (nausea/vomiting; fatigue, lassitude, dizziness, difficulty sleeping) All symptoms of mild intensity	Headache + 1 or more other symptoms (nausea/vomiting; fatigue, lassitude, dizziness, difficulty sleeping) All symptoms of moderate – severe intensity	Worsening of symptoms seen in moderate–severe AMS
Signs	None	None	Ataxia, severe lassitude, altered mental status, encephalopathy
Lake Louise AMS Score (12) (*see* Table 18.4)	2–4	5–15	Not applicable

Source: Reference [17]

successfully adjusted to a given altitude are said to have acclimatised. 'Adaptation', by convention, is used to describe physiological changes occurring in a population over generations.

Symptoms and signs

Headache is the cardinal symptom of AMS, although it may be absent in up to 5% of studies diagnosing AMS [10]. It is non-specific, commonly being bilateral, frontal, temporal or diffuse, dull or pressing in nature and often worsened by movement, exercise, bending down, coughing or sneezing [11]. Other forms of headache such as migraine are also possible at altitude and may even be triggered by it. Symptoms are many, the commonest being listed in Table 18.5, but can also include difficulty concentrating, irritability, feeling depressed or moody, and feeling chilly [10].

Symptoms typically appear within 6–12 hours, but can be up to 24 hours, of abrupt height gain and, if no further ascent is made, will usually settle within 2–3 days without recurrence at that altitude. They may, however, occur on further movement to higher altitude. Short sojourns of an hour or two such as transiting a high pass by bus before return to low altitude are thus unlikely to lead to AMS.

Signs are few and are not diagnostic for AMS. There is no difference in respiratory rate or blood pressure between those with or without AMS [12]. An increase in temperature of 0.5°C in mild AMS, 1.2°C in more severe AMS and 1.7°C in HACE was found in one study [13], whereas another found a decrease in temperature with AMS at rest [14]. Peripheral oedema is common at altitude, occurring in 18% of trekkers at 4,243 m in one study. Of these, 64% had and 36% had not got AMS [15]. Lung crepitations may accompany AMS or indicate developing HAPE, but are also found in asymptomatic climbers [12, 15]. By definition, neurological signs are absent in AMS so development of ataxia, severe lassitude, change in behaviour, altered mental status or encephalopathy indicate progression to HACE (Table 18.4) [16, 17]. HACE can, however, present with focal neurological symptoms and must be considered in the differential diagnosis following any recent rise in altitude [18].

The non-specific symptomatology may cause diagnostic difficulty with other disorders such as dehydration, alcohol hangover, exhaustion, hypothermia, hyperthermia, hypoglycaemia, diabetic ketoacidosis or migraine, which may of course co-exist, or with less common illness such as stroke/transient ischaemic attack, carbon monoxide poisoning (especially if cooking inside tents or enclosed huts), etc. [19]. Onset of symptoms more than 3 days after arrival at a given altitude, absence of headache and failure to improve with oxygen, descent or dexamethasone (see below) would tend to indicate a non-AMS diagnosis [19].

Measuring and diagnosing AMS

In 1993, a consensus group meeting in Lake Louise defined AMS using a simple five-question, self-report scoring system (Table 18.4) in order to facilitate comparison between studies [20]. As this score is so much easier to use than others, such as the longer 67 question Environmental Symptom Questionnaire [21], it is readily adopted by trekkers and mountaineers. Any scoring system can under- or over-diagnose; a hangover at sea level, for example, would produce a positive AMS score. So for this reason the score must be used in the context of a recent rise in altitude and consideration made for any confounding illnesses. For a diagnosis of AMS by Lake Louise Score there must be a recent rise in altitude, there must be a headache, at least one other symptom from

the list, and the total score from adding the response to each of the questions must equal 3 or more. (Some studies use a score of 4 or more, which gives a sensitivity of 78% and specificity of 93% [22].)

Differentiating AMS from the other causes of ill health in preverbal children is difficult but is facilitated by the Children's Lake Louise Score. This replaces the headache question with a 'Fussiness' score with additional scores of eating, playfulness and sleep. Fussiness is defined as irritability without obvious cause such as hunger, teething or pain from an injury [23, 24].

Epidemiology

Several factors influence the incidence of AMS and HACE. Foremost are rate of ascent, consequent altitude attained and individual susceptibility (Table 18.6). It appears to be sleeping altitude that is most important rather than short forays above this, and typically is much more likely to occur above 2,500 m but can occur lower in some. Risk factors are living altitude below 900 m [4], exertion on arrival at altitude [25], obesity – at least in men [26], in one study obesity increasing risk up to 3 times [27]. Some studies show increased risk in males compared with females, others show equal incidence [4, 12, 28]. Children and adults seem equally at risk [23, 24, 29], though the over-50s appear to have slightly reduced incidence compared with younger adults [4, 28, 30].

Trekking companies often hire lowland locals as porters and thus they are susceptible to the effects of altitude like the lowland tourists they serve [31].

Unfortunately there are no firm sea level predictors of performance at altitude although there is intra-individual consistency. Anyone can develop AMS if ascent is too rapid, but for any given altitude and ascent profile some are particularly susceptible. Past performance is the best predictor, but even good acclimatisers can develop AMS if ascending too rapidly or with additional factors such as intercurrent respiratory infection. Importantly sea-level athletic fitness is not protective of AMS [32] and indeed may be a predisposing factor by enabling a more rapid ascent.

These varying factors account for the wide range of AMS incidence reported in the literature (Table 18.6). The incidence of HACE is much lower, at around 0.1–4%.

Pathophysiology

In contrast to the well-established and accepted underlying pathophysiology of HAPE (discussed below) the precise pathophysiology of AMS and HACE remains less clear. Cerebral oedema and elevated intracranial pressure (ICP) are present in severe AMS and HACE, although it remains

Table 18.6 Incidence of AMS in various studies

Study	Location	Subjects	n	Altitude (m)(approx)	% with AMS
Hackett (1976) [28]	Nepal	Unacclimatised trekkers:	278	4,243	53 overall
		Walked from Kathmandu			42
		Flew to 2,800 m			60
Montgomery (1989) [33]	Colorado	Conference delegates	454	2,000	25
Montgomery (1989) [34]	Colorado	Conference delegates	35	2,700	40
Dean(1990) [35]	Colorado	Conference delegates	100	3,000	42
Theis (1993) [29]	Colorado	Denver children age 9–14 at camp	558	2,835	28
Maggiorini (1990) [12]	Swiss Alps	Climbers	466	2,850	9
				3,050	13
				3,650	34
				4,559	53
Honigman (1993) [4]	Colorado	Tourists within 48 h of arrival	3,158	1,900–2,900	25 overall
				1,800–2,100	18
				2,100–2,700	22
				>2700	27
Murdoch (1995) [36]	Nepal	Tourists flying direct to altitude	154	3,740	84
Davies (2009) [37]	Tanzania	Kilimanjaro trekkers on summit day	181	5,895	77 overall
Wu (2009) [38]	Tibet	High-altitude railroad construction workers	600	4,292–4,779	59

uncertain whether the observed oedema is cytotoxic (due to fluid shifts into cells) or vasogenic (resulting from increased permeability of the blood–brain barrier) in origin. Cerebral oedema and intracranial hypertension do not appear to play a role in milder forms of AMS as limited studies have failed to show any evidence of increased ICP in such patients. A 'tight-fit' hypothesis has been proposed in which susceptibility to AMS is thought to be a function of the individual's ability to shift cerebrospinal fluid (CSF) out of the cranium or handle increases in cerebral volume. This hypothesis fits with the observation that older individuals who likely have age-related brain changes that allow room for swelling without increases in ICP may be less susceptible to AMS [39]. Other proposed explanations for milder forms of AMS include peroxidative stress, abnormal cerebrovascular reactivity or neuropeptide responses, and hypoxia-induced changes in blood–brain barrier permeability that alter transit of plasma compounds causing neurotoxicity or irritation [40]. Mechanisms outside the central nervous system, such as alterations in salt and water homeostasis due to altered atrial natriuretic peptide or aldosterone levels or renin-angiotensin system activity [41, 42], may also contribute to the development of these disorders.

Treatment

Rest alone, with adequate hydration and of course no further ascent until well, are sufficient for mild AMS. Analgesics such as codeine, paracetomol or aspirin are often used but lack randomised trials of effectiveness. Ibuprofen is more effective than placebo in relieving headache [43], although altitude appears to increase risk of gastrointestinal bleeding so caution is required in its use [27]. Antiemetcs offer symptom relief. Should AMS progress to moderate or severe, then descent is the primary treatment and the affected individual should not reascend until the symptoms resolve. Typically 300–1,000 m is effective. Acetazolamide and dexamethasone are effective [44] (Table 18.7). Oxygen at a flow rate sufficient to produce a SpO_2 of >90%, where available, is likely to be limited but is useful especially where the terrain or weather makes immediate descent unfeasible.

Treatment of HACE requires immediate descent, dexamethasone and oxygen if available. Acetazolamide is often also given as an adjunct (Table 18.7). Portable hyperbaric chambers simulate descent (by as much as 2,000 m when used at 5,000 m), are effective for severe AMS and HACE, and are useful when descent is not possible or delayed or while awaiting evacuation, but should not be a substitute for descent [45–47]. Symptoms may recur following exit from the chamber so use should not delay descent where this is immediately possible [48]. It is important that individuals descend accompanied by a same-language companion, especially in cases of HACE [17].

Table 18.7 Pharmacological treatment and prophylaxis of AMS and HACE

Disorder	Drug	Prevention	Treatment
AMS	Acetazolamide	125 mg bd	250 mg bd*
	Dexamethasone	2 mg qds/4 mg bd	4 mg qds
HACE	Dexamethasone	2 mg qds/4 mg bd	8–10 mg stat then 4 mg qds

*Acetazolamide can be used in HACE as an adjunct to dexamethasone but dexamethasone has priority.

Prevention

Given that rapid ascent to too high an elevation is the main risk factor for developing AMS and the other high-altitude illnesses, the single best way to prevent altitude illness is to undertake a gradual ascent to the target elevation. According to guidelines released by the Wilderness Medical Society, above an elevation of 3,000 m, individuals should not increase their sleeping elevation by more than 500 m/day and should include a rest day every 3–4 days during which they sleep at the same elevation for at least one extra night [17]. This specific protocol has not been tested in a controlled manner and is largely based on consensus opinion, although several recent prospective trials have supported the role of graded ascent in the prevention of altitude illness [49]. Graded ascents may also affect the magnitude of observed physiologic responses to acute hypoxia, such as pulmonary artery pressure responses [50].

How long acclimatisation is retained following descent will largely be a function of the duration of time spent at a given altitude. Individuals who were only at altitude for a short period of time may retain little benefits after only a few days following descent and will need to go slowly to altitude with subsequent ascents, while individuals who had been at a given altitude for a long period of time (e.g. several weeks) will retain their acclimatisation longer and may reascend more quickly to altitude, provided they were not down at low elevation for too long.

Some studies suggest that chronic intermittent hypoxia exposure in lowlanders over months or years, such as in high-altitude mine workers in Chile or railway construction workers in Tibet, offers limited protection [38]. Even

exposures to high altitude over much shorter time frames (e.g. 5 or more days above 3,000 m within the previous 2 months) may affect susceptibility to AMS [51].

Drugs used in treatment and prevention

While non-pharmacologic measures work well in certain situations for prevention of altitude illness, in other situations, pharmacologic options should be considered. In general, the decision as to whether to use pharmacologic prophylaxis should be based on the risk associated with a given ascent profile. Risk can be classified according to criteria specified by the Wilderness Medical Society Guidelines for the Prevention and Treatment of Altitude Illness (Table 18.8). Individuals undertaking low-risk ascents can generally forego pharmacologic prophylaxis while those undertaking moderate- or high-risk ascents should strongly consider this option [17].

The standard prophylaxis regimens for AMS and HACE are described in Table 18.7.

Table 18.8 Risk categories for acute mountain sickness [17]

Risk category	Description
Low	• Individuals with no prior history of altitude illness and ascending to ≤2,800 m • Individuals taking ≥2 days to arrive at 2,500–3,000 m with subsequent increases in sleeping elevation <500 m/day and an extra day for acclimatisation every 1,000 m
Moderate	• Individuals with prior history of AMS and ascending to 2,500–2,800 m in 1 day • No history of AMS and ascending to >2,800 m in 1 day • All individuals ascending >500 m/day (increase in sleeping elevation) at altitudes above 3,000 m but with an extra day for acclimatisation every 1,000 m
High	• History of AMS and ascending to ≥2,800 m in 1 day • All individuals with a prior history of HAPE or HACE • All individuals ascending to >3,500 m in 1 day • All individuals ascending >500 m/day (increase in sleeping elevation) above >3,000 m without extra days for acclimatisation • Very rapid ascents (e.g. <7-day ascents of Mt Kilimanjaro)

Acetazolamide (Diamox) is a diuretic causing respiratory stimulation by alkaline diuresis-induced metabolic acidosis as well as central effects on respiratory control centres [52]. Because it contains a sulfa moiety, individuals with documented sulfa allergy must take caution with acetazolamide. Although the risk of cross-reactivity is low, cases of anaphylaxis have been reported in patients with documented sulfa allergy who received acetazolamide, and the remote mountain regions of the world are not the place to find out that someone is one of the rare people who does cross-react. For that reason, individuals with documented sulfa allergy who wish to use pharmacologic prophylaxis should undertake a supervised trial of the medication prior to their departure or consider using dexamethasone instead [53]. Nuisance side effects include paraesthesias, and carbonated drinks taste flat.

Dexamethasone has all the risks of potent steroids but importantly, unlike acetazolamide, it does not enhance acclimatisation. Theoretical concerns have been expressed about abrupt cessation of dexamethasone leading to appearance of symptoms of AMS or HACE but this issue has never been studied. Use of dexamethasone should be limited to <10 days to prevent glucocorticoid toxicity or adrenal suppression [17].

There are conflicting trials of the effectiveness of Ginkgo biloba [54–56], possibly arising from variances in composition of available preparations. It is not currently recommended. Coca leaves and coca tea are commonly advocated for AMS prophylaxis in South America but lack adequate trials and should not substitute for established methods.

High-altitude headache and other neurologic disorders at high altitude

Even among those who do not develop the full spectrum of symptoms associated with AMS, headache is a common complaint at high altitude. The International Headache Society defined high-altitude headache as a headache that develops within 24 hours following sudden ascent to altitudes >3,000 m and is associated with at least one other symptom associated with high altitude, including central sleep apnoea, a desire to over-breathe or exertional dyspnoea [57], although this definition has been criticised because such headaches can occur at lower elevations (2,000–3,000 m) and the associated symptoms are often lacking [42]. Isolated headaches may occur in as many as 83% of people who ascend to elevations of 5,100 m. The frequency may be lower in older individuals while the severity appears to be increased in women and those who experience headaches regularly in their daily life. The clinical features vary considerably between individuals, with the most common pattern being

a bilateral, generalised ache that is worsened by movement or exertion and often comes on at night [58]. Non-steroidal anti-inflammatory agents, acetaminophen/paracetamol and standard AMS prophylaxis agents are all effective agents for both prophylaxis and treatment, although spontaneous resolution is often seen within 24 hours.

A variety of other neurologic conditions have also been described at high altitude including transient ischaemic attacks, cerebral venous thrombosis, seizures, syncope, delirium, cranial nerve palsies, cortical blindness and amaurosis fugax [59]. Descriptions of these problems are largely restricted to case reports and small case series and no studies have systematically established that the risk of these disorders is increased in this environment. In general, the onset of neurologic symptoms that do not appear to fit the standard features of AMS or HACE and which do not resolve quickly with supplemental oxygen should prompt descent to lower elevation for further evaluation. Attempts should not be made to manage such situations while remaining at high altitude unless the weather or other logistical factors preclude evacuation.

Sleep at high altitude

Difficulty sleeping is also a very common problem at high altitude with some studies reporting incidence rates of as high as 71–93% in individuals ascending to 4,200 m without the aid of pharmacologic prophylaxis against altitude illness [60, 61]. Subjective complaints typically include problems with sleep maintenance, frequent awakenings and vivid dreams, while other studies have documented more objective evidence of sleep disturbances including increased number of arousals, increased periodic breathing (also referred to as Cheyne Stokes respirations), and sleep architecture changes including increased time in stage I sleep and variable changes in the duration of REM sleep [62]. Periodic breathing, which can occur even during wakefulness in drowsy individuals, is thought to occur as a result of instability in the respiratory control centre during sleep and is exacerbated in those individuals with strong hypoxic ventilatory responses. Although subjective impressions of sleep quality may improve over time at a given elevation, periodic breathing can persist for long periods of time and may even increase in severity with acclimatisation [63, 64]. To avoid problems with overmedication on a high-altitude sojourn it is probably best to avoid sleep medications if possible, despite the problems noted above. In situations where sleep difficulties have the potential to interfere with daytime performance, important tasks or enjoyment of the trip, pharmacologic therapy may be warranted. Four medications – acetazolamide, temazepam, zaleplon and zolpidem – have been studied at high altitude and shown to improve various aspects of sleep without impairing daytime performance. Diphenhydramine and eszopiclone, two commonly used sleep medications at sea level, have not been studied at high altitude but are likely safe given their mechanism of action and side-effect profile, while long-acting benzodiazepines such as diazepam or opiate pain medications should not be used for this purpose due to their potential to cause hypoventilation [65].

High altitude pulmonary oedema

High-altitude pulmonary oedema (HAPE) is a non-cardiogenic form of pulmonary oedema that affects travellers to elevations above 2,500 m. The disorder is potentially fatal if not recognised and treated promptly, and can occur in conjunction with AMS and HACE, or in isolation.

Epidemiology and risk factors

HAPE affects between 0.2% and 15% of individuals ascending to elevations as high as 5,500 m, depending on rate of ascent and the ultimate altitude achieved [66, 67]. In individuals known to be susceptible to the disorder, referred to as 'HAPE-susceptible', the rate of recurrence with subsequent ascent is roughly 60% [68].

The majority of cases occur in unacclimatised lowlanders ascending to high elevation, but cases of 're-entry HAPE' have also been described in which high-altitude dwellers develop pulmonary oedema on returning to high altitude after a sojourn to lower elevations. Recent work also suggests that as many as 75% of climbers to elevations as high as 4,559 m may develop asymptomatic subclinical extravascular pulmonary fluid accumulation, although this result has not been validated in further studies [69].

As with AMS and HACE, the main risk factor for HAPE is an overly rapid ascent to a given high elevation. Individual susceptibility also appears to play an important role, as individuals with a history of the disorder demonstrate exaggerated pulmonary vascular responses to hypoxia and exercise in both normoxia and hypoxia when compared with people with no history of the disorder [70, 71]. They have also been shown to have a reduced hypoxic ventilatory response at altitude, which contributes to the vascular reactivity by causing a lower alveolar PO_2 and, as a result, a stronger stimulus for hypoxic pulmonary vasoconstriction [72]. Beyond these HAPE-susceptible individuals, who are otherwise generally healthy, additional evidence suggests that individuals with underlying pulmonary hypertension due to both anatomic and non-anatomic abnormalities may be susceptible to the disorder [73]. Other studies suggest antecedent respiratory viral infections or the presence of a patent foramen ovale [74] may also increase risk, although the

causal mechanism for these possible relationships has not been adequately established.

Pathophysiology

A marked rise in pulmonary artery (PA) pressure following ascent is the key pathophysiologic feature of HAPE. While all individuals experience a rise in PA pressure in acute hypoxia, people who develop HAPE demonstrate exaggerated responses in which a marked rise in pulmonary vascular resistance and PA pressure lead to increased pulmonary capillary hydrostatic pressure. This subsequently causes increased capillary permeability and, in severe cases, capillary stress failure, which promotes transit of blood, protein and fluid from the vasculature to the interstitial and alveolar spaces. The precise mechanisms underlying this pulmonary vasoreactivity have not been identified but may relate to underlying differences in the balance between vasodilatory and vasoconstricting mediators, including nitric oxide and endothelin. While earlier bronchoalveolar lavage (BAL) studies on HAPE patients revealed elevated levels of inflammatory mediators in the lavage fluid suggesting that inflammation was an important underlying mechanism [75], subsequent studies have revealed the early stages of HAPE to be a largely non-inflammatory process [76]. Additional work has suggested that alterations in trans-alveolar sodium and water transport may also play an important role in disease pathophysiology [77].

Clinical presentation

HAPE occurs within 2–5 days of ascent to a given elevation. In the early stages of the disease, individuals develop increased dyspnoea on exertion and a dry cough, often requiring frequent rest breaks and increasing amounts of time to recover during breaks relative to well travel partners. As the disease worsens, dyspnoea becomes evident with simple activities such as walking on flat ground or changing clothing, while in the very late stages individuals have profound fatigue, dyspnoea at rest and may cough up pink, frothy sputum.

Physical examination demonstrates low-grade fever, tachycardia, tachypnoea, crackles on lung examination and peripheral cyanosis. Patients may also have concurrent symptoms and signs of AMS or HACE. Pulse oximetry and, when available, arterial blood gas analysis, demonstrate hypoxaemia with oxygen saturation and arterial PO_2 values lower than those of healthy individuals at the same elevation. Chest X-rays and computed tomography (CT) scans reveal patchy peripheral opacities early in the disease and more diffuse, homogenous infiltrates as disease severity worsens. Electrocardiography typically reveals a sinus tachycardia with possible evidence of right heart strain, right axis deviation or right bundle branch block. Recent work suggests chest ultrasonography, and the identification of 'comet tails' – ultrasonographic markers of interstitial fluid accumulation – may be useful in diagnosing HAPE in remote settings, but further validation of the technique is necessary [78].

Prevention

As with AMS and HACE, the single best way to prevent HAPE is to undertake a gradual ascent to the target elevation. Individuals should adhere to the same ascent rates recommended for AMS and HACE prevention and should also avoid heavy exertion early in their sojourn as this can contribute to excessive PA pressure elevation. Pharmacologic prophylaxis is recommended for people with a prior history of the disorder. Nifedipine (30 mg of the sustained-release version twice daily) remains the mainstay for prophylaxis, although recent work suggests that tadalafil (10 mg twice a day) and perhaps even dexamethasone (8 mg twice a day) may also have a beneficial role. Further work is needed to confirm these findings, however, and the latter two medications are not currently part of standard prophylaxis regimens. The long-acting beta-agonist salmeterol has also been shown to prevent HAPE in known susceptible individuals but should only be used as an adjunct to another agent and not as monotherapy.

Treatment

Effective treatment entails increasing alveolar oxygen tensions and alleviating the pulmonary arterial hypertension driving oedema formation. In remote settings, affected individuals should descend to lower elevations, with care being taken to avoid heavy exertion during evacuation. If descent is not possible for logistical reasons, treatment with supplemental oxygen or a portable hyperbaric chamber should be initiated. Patients should also be started on nifedipine (30 mg of the sustained-release version twice a day). Given their pulmonary vasodilatory properties, sildenafil and tadalafil should also be effective treatment options but no studies have evaluated their utility in this regard. Combination therapy with multiple pulmonary vasodilators should be avoided due to the risk of provoking systemic hypotension. There is also no role for inhaled beta-agonists or diuretic therapy.

When patients are able to access medical facilities, treatment with bed rest and oxygen may be sufficient and evacuation to lower elevation may be unnecessary. In well-selected patients with mild disease and adequate support (family, friends) to monitor their clinical course, it may even be

feasible to send them to their hotel with supplemental oxygen rather than admitting them to the hospital [79]. Patients who worsen or fail to improve with conservative measures should be started on pulmonary vasodilator therapy (e.g. nifedipine) and consideration can be given to initiating continuous positive airway pressure (CPAP) therapy.

Other altitude-related conditions

Aside from the main forms of acute altitude illness described above, several other medical conditions commonly affect travellers to high altitude.

Peripheral oedema

Oedema of the hands, lower extremities and periorbital area can develop as part of AMS, but can also occur in those who are otherwise tolerating altitude without difficulty. Treatment is not necessary and resolution occurs with descent, although individuals can try low-dose diuretic therapy for symptomatic relief.

Thromboembolic disease

Numerous case reports document the occurrence of arterial and venous thrombosis at high altitude but no systematic studies have revealed evidence of increased risk for thromboembolism in this environment. As a result, there are no indications for individuals to initiate anticoagulation regimens at high altitude if they are not already on such therapy prior to their sojourn. Instead, all travellers should be vigilant about maintaining hydration and mobility during their travels.

Cough

Dry hacking cough is a very common phenomenon among trekkers at high altitude. Typically non-infectious in nature, it likely develops as a result of changes in cough receptor sensitivity and the fact that individuals are breathing large volumes of dry, cold air, which irritates airway mucous membranes. The cough is bothersome and notoriously difficult to treat, has been associated with development of rib fractures in severe cases, and usually resolves with descent. Affected individuals may try throat lozenges, steam treatments or placing a balaclava or bandana across the nose and mouth to warm and humidify incoming air.

Respiratory infections

Studies have not established an increased risk for respiratory infection at high altitude. However, because many people travel in large groups or sleep and dine in close proximity to others, respiratory infections spread easily among travellers, many of whom note the slow pace of symptom resolution at high altitude. Travellers should remain vigilant about good cough and hand hygiene and should expect slow resolution of symptoms until descent is initiated. Antibiotics are generally not indicated unless the individual has signs and symptoms suggestive of pneumonia (fever, sputum production, hypoxemia)

High-altitude retinopathy

Retinal changes including disc hyperaemia, venous dilation and tortuosity, and retinal haemorrhage are common following ascent to elevations above 4,000 m. While the majority of lesions are asymptomatic, retinal haemorrhages involving the macula can cause painless blank spots in vision. Individuals with symptomatic haemorrhages should descend to lower elevation where spontaneous resolution typically, although not always, occurs over a matter of weeks. Formal ophthalmologic evaluation is warranted following descent and it remains controversial whether affected individuals can safely ascend to high altitude in the future.

Other neurologic conditions

While HACE is the most commonly cited neurologic problem at high altitude, reports have documented the occurrence of other neurologic complications such as cerebral sinus thrombosis or cerebrovascular accidents. Seizures may be unmasked at high altitude in predisposed individuals not on seizure medications and a theoretical concern exists that space-occupying lesions may also expand in hypobaric conditions. In general, global encephalopathy or altered mental status at high altitude, particularly in the setting of preexisting AMS, should be managed as HACE, but individuals failing to respond to appropriate therapeutic measures or demonstrating focal neurologic deficits, fevers or meningismus should be evacuated to lower elevation for further management.

Travel to high altitude with pre-existing medical conditions

Given the increasing popularity of adventure travel and the prevalence of common diseases in the general population, such as asthma, coronary artery disease, diabetes and hypertension, it is highly likely that many travellers will have underlying medical conditions at the time of their sojourn. In some cases, the underlying condition may predispose to acute altitude illness, while in other cases acute exposure to

hypoxia may lead to worsening control or unanticipated complications of the disease.

Pre-travel assessment and counselling is necessary for many of these patients to ensure a safe sojourn. A detailed description of the various diseases and the associated risks of high-altitude travel is beyond the scope of this chapter and the reader is referred, instead, to reviews that address these issues in greater detail for patients with various underlying conditions [80], including lung diseases [81], cardiac diseases [82], diabetes [83], ophthalmologic problems [84] and renal disease [85]. In general, however, clinicians can use several questions to guide their pre-travel assessment of risk.

Does the underlying disease predispose to the development of acute altitude illness?

In general, few diseases increase the risk of acute altitude illness, but data do suggest that obese individuals may be at increased risk for AMS [4], while patients with underlying pulmonary hypertension may be at risk for HAPE [73]. Given data suggesting that S_pO_2 on arrival predicts subsequent development of AMS, patients predisposed to hypoxaemia might also face increased risk of acute altitude illness, although no studies have specifically addressed this risk.

Can the patient maintain adequate oxygenation on arrival at high altitude?

The most obvious group of patients to which this question pertains are those with underlying lung disease as the available data clearly suggest that patients with various lung diseases, including chronic obstructive pulmonary disease (COPD), cystic fibrosis, interstitial lung disease and restrictive lung disease, become hypoxaemic when exposed to hypoxic conditions. Patients with right-to-left shunt (e.g. congenital heart disease) may also be predisposed to this problem while patients with severe anaemia, despite having adequate arterial PO_2, may have poor oxygen delivery and impaired hypoxia tolerance.

Can the patient adequately raise their minute ventilation on arrival at high altitude?

As noted above, hypoxic ventilatory response (HVR) is an important response to acute hypoxia that helps defend alveolar and, therefore, arterial oxygen levels. Patients with underlying neuromuscular diseases such as Duchene's muscular dystrophy or patients with altered control of breathing (e.g. following carotid body injury or resection) may not be able to sufficiently raise their minute ventilation and, as a result, may develop severe hypoxaemia.

Will acute hypoxia worsen disease control or predispose to complications?

In certain patient populations, hypoxia or the physiologic responses to it can worsen underlying disease control. For example, increased sympathetic stimulation increases systemic blood pressure with considerable inter-individual variability in observed responses and may affect blood glucose control in diabetic patients. Similarly, hypoxic pulmonary vasoconstriction may lead to right ventricular dysfunction or ischaemia in pulmonary hypertension patients, while hypoxia may promote sickle crises in patients with sickle cell disease and exercise in hypoxia may provoke cardiac ischaemia in patients with untreated coronary artery disease.

Pre-travel assessment will be necessary to address these issues and may require various forms of testing (e.g. echocardiography, exercise treadmill testing) depending on the disease in question. When doubt persists about hypoxia tolerance, patients can undergo high-altitude simulation testing in which they breathe a low oxygen mixture (typically F_IO_2 0.15 for 20 minutes) while oxygenation and other physiologic responses are monitored [86]. Depending on the clinical circumstances, the degree of hypoxic exposure and duration of the test can be altered to provide more accurate assessment of the likely responses.

For patients deemed safe to travel to high altitude, plans should be arranged to monitor symptoms and react to problems should they develop. For example, patients with poorly controlled or labile hypertension should monitor their blood pressure responses, while diabetic patients may need to increase the frequency of glucose monitoring and should travel with plans for adjusting their blood pressure or diabetes medications as needed. Patients should travel with an ample supply of their baseline medications as well as medications necessary to respond to problems such as an asthma or COPD exacerbations. Finally, those patients opting to use medications for prophylaxis or treatment of acute altitude illness may need to alter the choice or dose of medication based on their underlying problem or the potential for drug–drug interactions [53].

HOT ENVIRONMENTS

Introduction

Travel often involves hot climates, whether this is arid desert climes that are hot and dry, or the hot and humid

environments of the tropics or jungle areas. These can be some of the most stunning and beautiful places on earth but they can also be a challenging place to live, work or travel through.

Desert environment

A desert is defined as somewhere that receives less than 250 mm precipitation per year; hence Antarctica is the largest desert in the world. Hot deserts are dominated by high daytime temperatures with low humidity and cloudless skies. There is often little shade and underfoot may range from hard-packed stony ground to sweeping sand dunes. At night temperatures plummet as the earth radiates back a lot of the heat gained in the day. Environmental considerations include difficulty finding water, lack of shade in the day and possible sandstorms. The distance from populated areas means that many expeditions are vehicle-based or have vehicle support. Reliable four-wheel drive vehicles with experienced drivers are needed. Communication needs to be planned beforehand; satellite phones often get good coverage. Casualty evacuation plans will often include aeromedical companies; there is a range of coverage. Sadly many deserts now are in areas of conflict, and expedition safety must always be a priority.

Jungle environment

The high vapour pressure or humidity makes jungle living more of a challenge for many. The reduction in efficiency of sweating increases the risk of heat-related illnesses and minor ailments. Jungles are hot and humid in the day with often little respite at night as the humidity, along with heavy canopy or undergrowth, insulates the earth. Underfoot is predominantly wet. Dangers include water crossings, deadfall (broken or dead branches or trees that are caught up in the canopy originally but can come crashing down), hostile flora, venomous creatures and the use of machetes. Unfortunately, threats from human conflict or local illicit groups may actually be the biggest risk in some jungle areas. River-based vehicle support is likely to be a big part of casualty evacuation plans and creating landing zones for aeromedical support may be unfeasible.

Environmental and ethical issues

We must all be aware of the impact our travel makes on an area, both environmentally and in terms of disruption to local communities, and make efforts to minimise any negative effect. Plastic waste from bottled water is a huge environmental burden in developing countries. We must endeavour to use alternative water sources and filter and/or treat it so that it is safe to drink. Altering local trading and taking away resources can have a major impact on remote communities. Ethical considerations must be thought through before arriving. These should include the extent we impose our values onto local team members, e.g. regarding drugs or alcohol, and the circumstances in which the expedition would use its medical resources to treat other local people.

Thermoregulation

Physiology of thermoregulation

Average human core temperature is 37.1°C and the body has complex and highly accurate systems aiming to keep this constant. Central and peripheral thermoreceptors detect any rise in blood temperature and the hypothalamus controls hormonal responses. Circadian rhythms give lower temperatures in early mornings and higher readings in the afternoons, peaking around 4pm. Body shape is important. The Kenyan Masai are ideally built for hot climates; they are tall and slim with a large surface area to mass ratio. Compare this to the Inuits, who are built to insulate themselves against the cold of the Arctic.

Heat transfer

There are four methods of heat transfer.

1 Conduction is the passing on of heat energy through physical contact, e.g. feet on hot ground.

2 Convection is transfer of heat energy into a fluid or a gas, usually from skin to air that is circulating around the body. Some heat is lost into air from the respiratory passages and also into urine and stools. Convection via circulating blood from the warmer core, along with conduction through tissues, keeps the temperature throughout the body relatively constant.

3 Radiation is direct transfer of infrared heat down its gradient and this is the main method of heat loss in temperate climes. If environmental temperature is higher than skin temperature (usually around 32°C), the body can absorb heat from the environment.

4 Evaporation involves the conversion of a liquid (sweat) to a gas. Sweat absorbs heat from the skin in order to vaporise; this is increasingly important in hot environments.

Behavioural and vasomotor changes

The body employs three main mechanisms to maintain a steady core temperature. The first two act synergistically – behavioural and vasomotor responses. We have strong instincts to maintain homeostasis and if body temperature starts to rise we are driven to seek shade, remove layers of insulating clothes or put extra on to protect from high solar radiation and to correct any dehydration. Vasomotor changes, namely vasodilation, divert warmer blood from the core up towards the surface of the skin. Arterial dilation allows more blood up to the surface and venodilation keeps it there for longer, increasing heat losses through radiation and convection. Skin blood flow at 37°C is around 250 ml/minute and increases linearly as body temperature rises, up to a maximum of 6–8 litres/minute [87]. This is a rapid and very accurate way of managing heat dissipation. This increased blood flow can take up to 60% of cardiac output, leading to a reduction in blood flow to the bowel and splanchnic region. There is an increase in stroke volume, and in particular in heart rate [87, 88].

Sweating

If maximum vasodilation and behavioural changes do not control the rising body temperature, the third mechanism – sweating – commences. Sweat glands are modified hair follicles found all over the body. There are between 2 and 4 million of these eccrine glands and the vast majority are under sympathetic control [88]. Sweating on the palms of hands and soles of feet is under autonomic control. Sweat glands are densest over the head, face and neck, and upper torso and back [89]. Their valves open cyclically, allowing controlled amounts of electrolyte-rich water onto the surface of the skin. The sweat absorbs heat from the skin below it as it vaporises; one litre of sweat evaporating absorbs 580 kcal energy [88, 90]. If the vapour pressure (humidity) of the air is too high it may not be possible for sweat to evaporate and it may simply roll off the skin. In this instance it takes little heat with it and is the reason that humid environments are more challenging to the body. While engaged in strenuous exercise sweat rates of more than 1 litre/hour are common and a high of 3.4 litre/hour has been recorded. Replacing this fluid becomes increasingly difficult at higher sweat rates, as it is rare for most people to be able to absorb more than 1 litre/hour [91].

Heat stress

This concept is used within sport and exercise in the heat and can help raise awareness of the risk of heat-related illnesses. The heat load at any one time depends on the metabolic heat from within the body plus environmental heat, and is balanced by heat dissipation. The vast majority of heat produced is as a result of muscle contractions. Several heat stress indexes have been formulated to guide organisations regarding levels of activity recommended in the heat, but few are practical to use. Wet globe bulb temperature (WGBT) has been used a lot by the military as a guide to suitable levels of exertion under particular conditions, but it needs the specific equipment to give a WGBT reading and takes 30 minutes to calibrate. An environmental stress index using ambient temperature, relative humidity and solar radiation can be worked out using small hand-held microsensors. However, a physiological heat index using heart rate, rectal temperature and humidity gives a more accurate reflection of heat stress to an individual [92–94].

Children

Infants are particularly susceptible to heat illnesses as they cannot verbalise any discomfort or regulate their own clothing layers or environment. Children have a smaller body surface area to mass ratio. They have the same vasomotor responses as adults but a more limited ability to sweat. Mobilisation of sweat glands in the axillary and groin areas occurs with puberty.

Older people

After approximately the age of 60 the vasomotor responses of the body become less accurate. Cardiac conditions that reduce the ability to increase heart rate or stroke volume to match vasodilation or sweat levels impair the body's reaction to heat stress. Many medications (*see* Table 18.10) can also interfere with thermoregulation. Acclimatisation takes longer in older people but this may simply be as a result of reduced initial fitness levels. Older individuals produce fewer protective heat shock proteins, so there is less tolerance to a sustained rise in body temperature [92, 95].

Women

Once surface area to mass ratios have been taken into consideration there is little difference between men and women. Women have a higher (up to 0.7°C) core temperature during the luteal half of the menstrual cycle, between ovulation and menstruation, which gives a little less leeway with regard to heat-related illnesses. Women also have a slightly reduced maximum sweat rate. The autonomically instigated hot flushes of menopause add to heat stress and can prove difficult to deal with in hot environments. During pregnancy the body's average core temperature actually

drops, particularly in the final trimester and hence heat-losing mechanisms will commence at an earlier stage in the heat. This is to protect the fetus from heat stress, as this is associated with a small increased risk of neural tube defects [92].

Sanitation

If people are not keen to use camp toilets or perform in the open they often reduce their fluid intake to reduce the frequency of using such facilities. Equally, if trekking for a day in open desert, for example, there is little privacy available and again individuals may try and reduce the need for ablutions in the day. Education early in the expedition is vital.

It is important that women on an expedition know what facilities there are for sanitation. Used sanitary products should be wrapped and carried out in the day, ideally with a fire available at night to burn them. Dislike of facilities and lack of privacy can make people reluctant to change protection as frequently as usual but this must be overcome and the small risk of toxic shock syndrome highlighted.

Hydration

Fluid balance is extremely important in hot environments. Increased fluid is needed for efficient vasodilation and sweating. In particularly dry environments the respiratory passages may lose significant fluid humidifying air before it enters the lungs [89]. The thirst mechanism only commences once 2–3% dehydrated, i.e. with a loss of 2–3% body weight of fluid. Physical performance and mental agility have been shown to drop before this level of dehydration. The majority of individuals will be struggling significantly by the time they are 6% dehydrated [92].

As the body loses fluid, plasma osmolality (concentration) increases. This leads to a linear rise in production of antidiuretic hormone (ADH) from the pituitary. ADH, along with aldosterone from the adrenals, works within the kidney tubules reabsorbing sodium, which pulls water along with it and excretes potassium [88, 92, 96].

To maintain hydration the volume of fluid taken in needs to match the volume of fluid lost. Small amounts of water are produced as a by-product of metabolism, but the vast majority needs to be ingested as drink or within food. Water is absorbed from within the small intestines at variable rates, but most people are able to absorb up to 1 litre fluid/hour maximum due to gastric emptying limits. Significant volumes of fluid in the stomach while exercising leads to bloating and nausea; volumes tolerated can sometimes be increased with 'drinking training' [88, 96].

During sustained activity it is difficult to maintain hydration and most people will voluntarily replace two-thirds of lost fluid only. Much has been written on the best type of fluid for combating dehydration. At cellular level, water is absorbed via sodium-glucose cotransporters. However, there have been some studies showing that pure water can be absorbed just as quickly as that containing small amounts of glucose and sodium [97, 98]. If the osmolality of fluid is too high within the stomach absorption slows down [88, 91].

Many people find it difficult to drink large volumes of tepid water, particularly if it has been iodined for sterilisation, and may involve noticeable sand or grit each time a sip is taken. Adding neutralising tablets or flavour after full sterilisation has been completed improves palatability and encourages drinking. It has been suggested that drinking water with electrolytes rather than plain water can reduce the volume of fluid needed significantly to maintain a good work rate but this has not been proven in an expedition environment [99].

Dehydration

Signs and symptoms include nausea, headache, tiredness, malaise, irritability, reduced micturition and dark urine, plus or minus thirst, along with a raised heart rate, raised respiratory rate and reduced skin turgor. A very crude test of hydration is the ability to spit. If someone does not have enough fluid in their mouth to be able to spit on the ground, they are more than a few percent dehydrated. Many of these symptoms have not been shown to correlate in endurance athletes in a recent study, but unwell/collapsed athletes were not included [100]. One simple way to allow all team members to assess their own level of hydration is using urine colour. The darkness of urine has been shown to equate well to levels of dehydration and dark urine illustrates to people that however much they feel that they have drunk, it has not been enough for them that day [95, 101]. Many people use the analogy to aim for 'champagne pee'.

In the past, specific volumes of fluid to be ingested per hour have been recommended, but the 2005 Position Statement from the America College of Sports Medicine emphasised the need for individuals to assess their own fluid needs as there is large inter-personal variation [95]. The importance of initial health briefings in preparing a group to keep themselves well hydrated cannot be overemphasised.

Starting a day on expedition well hydrated is important and it is good to make sure everyone has an extra drink 30 minutes or so before setting off as well as a normal breakfast. Water bladders with tubes that clip onto rucksacks or are combined within rucksacks make it much easier to sip fluids

regularly. While trekking or cycling, this is much easier than having to stop or reach for water bottles inside packs. However, it is more difficult to assess how much has been drunk, and how much is left in the bag. Some groups use enforced stops and drinks as a way of ensuring an adequate intake within the group.

Oral rehydration

If someone is recognised as being dehydrated they need more fluid in. For mild dehydration simple water is usually enough, as long as people are eating too. With significant dehydration, coexisting diarrhoea or anorexia, oral rehydration salts (ORS) are quick to use. ORS has saved the lives of millions, particularly of children with diarrhoea, over the years. In 2003, WHO/UNICEF brought out a low-osmolality ORS consisting of 2.6 g sodium chloride and 13.5 g glucose per litre of water. It also contains potassium chloride and trisodium citrate. An equivalent fluid can be simply made up with one litre of treated water, ½ teaspoon of salt and 4 teaspoons of sugar [102]. Most commercial rehydration salts and some sports drinks utilise two different types of sugars (out of glucose, fructose, sucrose, maltodexrins) to maximise receptors usable for absorption. The glucose also begins to replenish carbohydrate reserves [97].

Hyponatraemia

This phenomenon is now recognised as a significant cause of morbidity and mortality in endurance races and has been linked to several deaths on expedition. Ingestion of large volumes of fluid without electrolytes leads to a reduction in plasma sodium. Risk factors include being female, low body weight, taking non-steroidal anti-inflammatory drugs (NSAIDs), being highly motivated, slow performance times and missing meals. There may be an element of inappropriate ADH secretion, but the volume of water drunk is always high [103]. Symptoms and signs are similar to dehydration, namely nausea, headache, fatigue, but often with bloating, pale urine and possible polyuria, so it is vital to take a good history. If not rectified, confusion, coma, seizures and death may follow. As long as regular meals are eaten there should be no need for electrolyte drinks or any sodium supplementation. Under some circumstances when high volumes of fluid are needed for high-intensity activity but no meals taken, fluid with electrolytes is recommended [91, 104]. Scales to accurately measure pre- and post-activity weight can be used to aid diagnosis; any weight gain will be due to excessive fluid intake. In the early stages, supporting the patient and withholding further fluid is usually enough to ensure recovery. In severe cases, 2.7% or 3% hypertonic saline has been used in hospital settings [103, 104].

Acclimatisation

The body acclimatises to hot conditions using several physiological methods. This usually takes 7–10 days and the bulk of this is lost within a few weeks of returning to temperate climes. The main physiological difference is that the threshold for heat-losing mechanisms is lowered. Hence, vasodilation begins earlier and sweating starts at a lower core temperature. Plasma volume is also increased. Sweat rate increases but the amount of sodium in the sweat becomes lower. This lower sodium increases the difference between the vapour pressure within the sweat and within the air, allowing faster evaporation and preservation of body sodium [92].

The best way to prepare for the heat is to do regular moderate- to high-intensity exercise in temperate conditions prior to heat exposure. When exercising, core temperature rises and the body then starts its heat loss mechanisms. Hence, regular 'sweaty' exercise trains these thermoregulatory mechanisms to kick in earlier. Hot baths and saunas can also aid acclimatisation to some degree. Once in the hot environment, gentle to moderate exercise will accelerate acclimatisation. Heart rate can be quite a sensitive reflection of heat stress and acclimatisation and is a simple method of monitoring heat stress and acclimatisation [88]. Exercise in the heat produces heat shock proteins. These protect tissues from the effects of heat making them more tolerant of higher temperatures [89].

Clothing

Clothing should be loose, to encourage frequent convective currents around the body, and pale in colour to absorb less solar radiation [89]. Tribes such as the Bedouin cover themselves completely so as not to absorb any solar radiation. Wicking materials help improve rapid heat loss and reduce dripping of sweat. In exposed conditions a hat will protect the face and eyes from the sun and, particularly in windy conditions, a scarf wrapped around the head can reduce sand and dust exposure. Good-quality sunglasses, ideally with side protection, should be used. Boots should be well fitted allowing some room for swelling. However, if they are too loose there is an increased risk of blisters.

Minor heat-related conditions

Sunburn

This often-underestimated and highly preventable condition is caused by insufficient protection from the electromagnetic radiation from the sun by way of clothing and sunscreen. On the earth's surface solar radiation consists of 90% ultraviolet

type A (UVA) and 10% ultraviolet type B (UVB). UVB absorption by the skin stimulates melanocytes, which tan and gives a cutaneous inflammatory reaction – sunburn, as well as producing vitamin D. UVA contributes a small amount to the tanning and burning processing, but penetrates more deeply and is the stimulus for some photoallergic drug reactions. Long-term risks of increased sun exposure include malignant melanomas (UVA), squamous and basal cell carcinomas (UVB) and cataracts (both). Sunscreen needs to be highly protective against UVA and UVB. It needs to be applied *before* any sun exposure and regularly reapplied [105]. The use of sun-protective clothing, including hats, increases protection enormously. Sunburn can seriously impair the performance of a team member. It also impairs vasomotor control and sweating, putting that person at a higher risk of a heat-related illness. The radiative heat transmitted from that portion of skin is uncontrolled and this abnormality continues for up to 7 days after the initial burn even if the redness goes [106]. Hence they are actually at risk of hypothermia within that week, for example if involved with water crossings.

Solar keratitis

Sand can reflect sunlight, and exposure of the eyes to solar radiation can damage the outer layer of the cornea. This gives painful, photophobic, red eyes. Treatment includes cycloplegics to reduce ciliary muscle spasm and topical antibiotics to prevent infection. In sandy or dusty environments, particularly in windy conditions, conjunctivitis, foreign bodies and corneal abrasions are all common problems. Protection, as previously mentioned, is vital.

Milia rubra

Prickly heat is the common name for this irritating skin condition. Usually occurring early in exposure to high temperatures, milia are a result of the rapid increase in sweating. Sweat glands block and there is a build-up of fluid below the blockage. This can cause intense irritation to the skin and impairs sweating. Thus there is an increased risk of heat-related illness. Prevention includes regular washing of skin and ventilation where possible. Treatment is with antihistamines if intolerably itchy and prevention of infection. The skin often desquamates 7–10 days later.

Heat cramps

Spasm of muscles that have been working hard is linked to mild hyponatraemia and the cooling of muscles. Hence this painful condition often occurs at the end of a long day's exertion, and when not enough electrolytes have been taken in. Treatment involves stretching and massage, along with replacing sodium in food or drink.

Heat syncope

Sudden loss of consciousness can occur, usually in the first few days of heat exposure, particularly when exertion has just stopped. When upright, 70% of the body's blood volume is below the heart. Gravity and vasodilation contribute to peripheral pooling of blood that occurs once the muscle pump has stopped; this, along with dehydration, can impair cardiac return. However, full consciousness should return within a few minutes of lying horizontally with legs held in the air. The victim must be checked for injuries and rehydrated. If they do not gain consciousness quickly a diagnosis of heat stroke must be considered and acted upon.

Heat oedema

Commonly, particularly in the early stages of exposure to a hot environment, gravity and vasodilation can lead to marked peripheral oedema – sausage fingers and toes. Finger oedema can be made worse by a heavy rucksack reducing lymphatic return. Significantly swollen feet increase the risk of blisters. No treatment is needed.

Skin problems and foot care

In humid environments, skin care becomes extremely important. Areas of friction can become chafed and infected, and wounds fail to heal. The constant sweating and wetness of the skin can exacerbate existing skin conditions and there is an increased risk of infection. Any cuts or abrasions should be treated early with antiseptic such as dilute iodine. Some medications, for example doxycycline, can cause photosensitive rashes, and exposure to certain plants containing psoralens can also cause a photoallergic rash.

On expedition, your feet are two of the most valuable possessions you own and need to be looked after well. In dry environments cracked heels can be extremely painful. Emollients and pumicing can help. Superglue can be used for large difficult cracks. Blisters can also be a huge problem. In sandy conditions it is difficult to prevent particles getting into socks and causing friction to the skin. Education about regular foot checks is vital. It is important to treat reddened tender areas (hot spots) early with a gel dressing such as Compeed and/or zinc oxide tape.

In humid conditions, particularly in the jungle, feet can become macerated and overrun by fungal infections. Trench foot can be a reality if you are in wet conditions daily. It is vital to have a good routine, including drying feet at night, keeping them dry and using topical antifungals. Pitting

keratolysis is caused by corynebacteria and gives a distinct set of black 'pits' on the soles of the feet, along with an unpleasant smell; it is successfully treated with clindamycin lotion.

Heat-related illnesses

Classic heat stroke

This heat-related illness happens over a period of time and does not involve exertion. It is unusual on expedition but can occur, for example while in non-air-conditioned vehicles or while marooned in a hot tent. Those at high risk are the very young, the elderly and those with pre-existing medical conditions that predispose them to dehydration or reduce their tolerance. Signs and symptoms are similar to exertional heat stroke, although there is rarely profuse sweating and no rhabdomyolysis. See Treatment on the next page. Ice fanning and immersion have similar outcomes [107].

Body temperature depends on:

Metabolic heat produced
+
Environmental heat load

vs Heat dissipated

Heat exhaustion

This is also known as exertional heat illness. In hot conditions, particularly when exercising, the body is faced with high metabolic and external heat loads, and its thermoregulatory mechanisms can be pushed to the limit. If heat gained is more than heat dissipated body temperature will continue to rise. Dehydration is often a contributory factor and there is always the balance of the fluid between that needed to maintain cardiac filling and to dissipate heat. If venous return is beginning to be compromised the body will shift fluid back from the periphery to the core, with subsequent reduced effectiveness of heat loss.

As shown in Table 18.9, there are many recognised risk factors for heat-related illnesses. Some are intrinsic and not open to alteration, but many others are subject to behaviour and expedition conditions and thus should be minimised. There is also some evidence of cumulative heat stress with the risk of exertional heat injury higher when the previous day's temperature and humidity were high [108].

There are also several medicines that increase the risk of heat-related illness (Table 18.10).

Signs and symptoms of heat exhaustion Fatigue, thirst, malaise, nausea, vomiting, diarrhoea, muscle aches or cramps, headache and dizziness. Casualties will have a normal conscious level but there may be subtle neurological changes such as poor coordination and reduced mental sharpness. Skin will be hot and sweating, mucosa dry, heart rate and respiratory rate raised. There may be a wide pulse pressure. Haematuria may reflect rhabdomyolysis.

Table 18.9 Risk factors for heat-related illness

Individual	Environmental	Situational
Poor fitness	High temperature	Dehydration
Obesity	High humidity	Poor acclimatisation
Diabetes mellitus	Low wind	Inappropriate clothing
Thyroid disease	High solar load and little shade	High exertion
Extremes of age	High temperature and humidity the previous day	Weight of pack carried
Skin disordersm e.g. scleroderma or ectodermal dysplasia		Fatigue
Previous or family history of heat-related illness		Missed meals
Certain medication (see Table 18.10)		Sleep deprivation
		Alcohol or drug intake
		Peer pressure
		High motivation
		Sunburn or milia rubra
		Intercurrent illness, e.g. fever, diarrhoea

Source: References [87, 96, 108]

Table 18.10 Medications that increase the risk of heat-related illness

Drug	Effect
Diuretics	Dehydrate
ACE inhibitors	
Alcohol	
Sedatives	
Haloperiodol	
Beta-blockers	Alter vasomotor response
Vasodilators	
Antidepressants (TCA, MAOI, SSRIs)	Increase metabolic heat generated
Thyroxine	
Amphetamines, cocaine, ecstasy	
Neuroleptics	Reduce sweating [92]
Anticholinergics	
Antihistamines	

Heat stroke

If heat exhaustion is not recognised and treated properly, body temperature will continue to rise and progression to

full heat stroke will occur. This is the extreme end of heat-related illness when the body stops compensating and systems begin to fail. There is a significant risk of mortality or neurological sequelae.

Heat stroke will have many of the similar signs and symptoms of heat exhaustion, temperature will be above 40°C and there is also a reduction in conscious level. It may present apparently out of the blue with a collapse and sudden loss of consciousness, or it may seem more insidious with confusion, disorientation moving onto coma with or without seizures. The casualty's skin will be hot and they may have stopped sweating, which is an ominous sign. This occurs more in very dry, windy conditions and with marked dehydration; however, an individual may still be sweating profusely and heat stroke cannot be ruled out simply due to the continued presence of sweating.

Above approximately 42°C, cellular derangement begins. The hypothalamus fails to recognise the increasing temperature as hot and, particularly if the body needs fluid to maintain cardiac venous return and output, sweating and vasodilation may stop. The person may feel cold and even start to shiver; autonomic dysfunction can give pinpoint pupils [103]. The combination of significant thermal insult plus ischaemia affects the bowel wall. It starts to lose its barrier ability and lipopolysaccrarides (LPS) leak out, giving a similar picture to sepsis. Above 43°C liver function begins to fail. Once clotting mechanisms start to dysfunction with resultant disseminated intravascular coagulation (DIC) mortality rates soar [90]. Rhabdomyolysis can lead to renal failure and compartment syndrome [109].

Treatment of heat exhaustion or heat stroke

All activity by the casualty must be stopped and shade found/constructed while full assessment occurs. Difficulty may lie in differentiating between loss of consciousness or seizure due to heat stroke and dehydration or to hyponatraemia; hence history, including from others, and examination for signs of dehydration are vital.

The aim of treatment is to bring down temperature as quickly as possible. The risk of death and of neurological damage is directly related to the time spent with extremely high body temperatures – the area under the curve with temperature over 40° and time on the axes [110]. If facilities allow, the most effective method of cooling the body is ice immersion and the use of this in certain military establishments, such as Parris Island, US, has reduced mortality significantly. However, this is unlikely to be available on expeditions. The casualty should be raised off hot ground, ideally in a hammock or on a camp bed, and stripped down to underwear. They need to be sprayed with water and fanned to aid convection currents. This should bring body temperature down. If ice is available this should be placed around the head and neck and in the groin and axillae. There are large blood vessels flowing just below the surface in the groin and axillae, and the heat and neck ice will help protect the brain and heart. When temperature within the brain is raised, blood flow reverses in the ophthalmic vein and flows back from the face to the brain bringing cooler blood centrally. Using ice or water-soaked towels over the body can also reduce temperature successfully [92, 107, 111].

If the casualty is thought to be dehydrated they should be rehydrated. If they are awake, oral rehydration fluid is helpful. Antiemetics will reduce nausea and vomiting. With any alteration in conscious level, fluid replacement must be intravenous and normal saline is suitable. There is a risk of cerebral or pulmonary oedema if this replacement is overzealous. Dextrose may be helpful to combat any hypoglycaemia [109].

It may be the case that someone's temperature does not reduce below a certain level despite effective cooling. This could be due to a raised temperature secondary to illness, but should never be assumed in the field; heat stroke is a medical emergency and while in-field treatment is continuing, plans must be made for evacuation. If clotting derangement occurs or if consciousness does not return despite temperature coming down below 39°C, prognosis is poor. It is also wise to assess rest of the group, as others could also be in difficulty.

Summary

Some of the most spectacular places to travel in the world are subject to extremes of heat, with or without humidity, which brings challenges. Sound preparation and early education of all team members is vital to make the expedition safe and keep the group healthy.

POLAR MEDICINE

Introduction

Although the world is a rapidly changing place, the polar regions still represent some of the most remote and hostile environments known to man. The challenge of remaining healthy within such regions is enormous. Initially the problems of surviving within the polar regions appear to be those extreme cold, wind chill, long-term cold, altitude and isolation. However, there are additional problems including sunburn, snow blindness, dehydration, carbon monoxide poisoning, sanitation, infection, trauma, aggressive wild

animals, communications and evacuation. Some polar journeys are lengthy and extremely arduous, and with limited access to a fresh, varied diet can result in weight loss, malnutrition, and issues around sanitation and hygiene.

Background

The polar regions are those parts of the world where the sun does not rise or set on at least one day a year. These regions are defined by the Artic and Antarctic circles at latitudes of 66° 33′ 39″ north and south respectively. Unlike altitude medicine or hyperbaric medicine, there is not a single unifying pathophysiology [92]. However, in terms of the principles and practice of travel medicine, the polar regions' challenges are those of extreme remoteness, cold and sometimes altitude.

The Artic and the Antarctic differ in that approximately 4.5 million people live within the Arctic circle while there are no indigenous peoples in Antarctica. Approximately 4,000 people will spend the summer in Antarctica and 1,000 the winter [1].

There are increasing numbers of visitors to the polar regions, made up of researchers and, more recently, tourists. Medical facilities vary, for instance within the Artic circle there are a number of towns of moderate size with medical centres and small hospitals equipped with investigational facilities and operating theatres. Antarctic bases have well-equipped medical centres that can deal with most intermediate medical problems, for instance all permanent US medical bases have digital X-ray and ultrasound facilities. Telemedicine is now widely available at many of these bases.

Researchers and scientists will often travel away from the bases for varying amounts of time and need to be self-contained. Expeditions will range in objectives, time spent on the ice, fitness and medical training of participants, communication equipment and support. The most recent development, polar racing, encourages individuals and groups of often limited polar experience to race over difficult terrain. Although there are usually supporting medical teams, clearly there are additional associated risks and potential problems. Remoteness and evacuation of individuals remain some of the greatest challenges. Medevacs are extremely costly and often dangerous, and there are Antarctic bases where no evacuation would be possible during winter. In view of the extreme remoteness, screening of polar travellers prior to travel to polar regions to pick up preventable or treatable medical and dental conditions is important.

While this chapter focuses on the aspects of cold and how it affects polar medicine, numerically the most common medical problems are trauma and infections. These are covered elsewhere within this book.

Physiology of cold

Thermoregulation

Humans are warm-blooded animals that are normally able to regulate their core body temperature at 37°C despite being exposed to a wide range of external temperatures. The ability to thermoregulate or maintain a set body temperature is an important component of homeostasis and involves the balancing of heat gain and heat loss [112]. Heat is produced as a result of metabolic activity primarily within the liver, heart, brain and skeletal muscles, and will increase production as a result of exercising or shivering. Brown fat accounts for variable non-shivering thermogenesis, particularly in children. Conversely, heat loss is a result of convection (10–15%), conduction (2–3%), radiation (55–65%), evaporation and respiration (20–25%). Skin and respiratory system are the major organs responsible for heat loss; each gram of water that vaporises consumes 0.58 kcal heat.

The human temperature control system has three distinct components. First there is an afferent input of temperature information from thermoreceptors. This information is then processed by the anterior hypothalamus and compared with the thermoregulatory set point (TRSP). Finally efferent responses result in the control of heat production or loss [112].

Thermoregulatory input comes from peripheral thermoreceptors in the skin and mucous membranes and central thermoreceptors in bone, spinal cord, brain and hypothalamus. The core temperature is then raised or lowered by a number of mechanisms (vasoconstriction, vasodilatation, thermogenesis), the aim being to keep temperature around 37°C to optimise enzymatic function.

In addition to the physiological components of thermoregulation, behavioural components will affect heat loss. Either dressing more warmly by putting on additional layers or removing layers will tend to affect temperature regulation. In addition, interactions with the environment changes will influence heat gain or loss. For instance getting into a tent or snow hole, putting a sleeping bag onto insulation since convective heat loss due to the wind chill factor is an important cause of heat loss (*see* Figure 18.4).

Hypothermia

Hypothermia is defined as a core temperature of <35°C. Core temperature measurement techniques are variable, with Alaskan guidelines [113] suggesting core temperature is best measured with an oesophageal temperature probe, whereas the European practice is to use epitympanic

T air	5	0	–5	–10	–15	–20	–25	–30	–35	–40	–45	–50
V_{so}												
5	4	–2	–7	–13	–19	–24	–30	–38	–41	–47	–53	–58
10	3	–3	–9	–15	–21	–27	–33	–39	–45	–51	–57	–63
15	2	–4	–11	–17	–23	–29	–35	–41	–48	–54	–60	–66
20	1	–5	–12	–18	–24	–30	–37	–43	–49	–55	–62	–68
25	1	–6	–12	–19	–25	–32	–38	–44	–51	–57	–64	–70
30	0	–6	–13	–20	–26	–33	–39	–46	–52	–59	–65	–72
35	0	–7	–14	–20	–27	–33	–40	–47	–53	–60	–66	–73
40	–1	–7	–14	–21	–27	–34	–41	–48	–54	–61	–68	–74
45	–1	–8	–15	–21	–28	–35	–42	–48	–55	–62	–69	–75
50	–1	–8	–15	–22	–29	–35	–42	–49	–56	–63	–69	–76
55	–2	–8	–15	–22	–29	–36	–43	–50	–57	–63	–70	–77
60	–2	–9	–16	–23	–30	–36	–43	–50	–57	–64	–71	–78
65	–2	–9	–16	–23	–30	–37	–44	–51	–58	–65	–72	–79
70	–2	–9	–16	–23	–30	–37	–44	–51	–58	–65	–72	–80
75	–3	–10	–17	–24	–31	–38	–45	–52	–59	–66	–73	–80
80	–3	–10	–17	–24	–31	–38	–45	–52	–60	–67	–74	–81

Where T air = Air temperature in °C and V_{so} = Observed wind speed at 10m elevation. in km/h.

FROSTBITE GUIDE
Low risk of frostbite for most people
Increasing risk of frostbite for most people in 10 to 30 minutes of exposure
High risk for most people in 5 to 10 minutes of exposure
High risk for most people in 2 to 5 minutes of exposure
High risk for most people in 2 minutes of exposure or less

Figure 18.4 Wind chill calculation chart. Courtesy of PGMJ review.

temperature measurement as the first choice. A low-reading rectal temperature remains the third choice.

Classification of hypothermia

Hypothermia can be primary or secondary. In primary hypothermia there is overwhelming cold exposure despite normal heat production. This is the most common cause of hypothermia in the outdoor environment. There are multiple causes of secondary hypothermia: hypothyroidism, burns, hypothalamic abnormalities, sepsis, drugs alcohol, etc. It is not uncommon to find hypothermic subjects with mixed primary and secondary hypothermia.

Mild hypothermia

Mild hypothermia (32–35°C) is associated with an increase the metabolic rate as a result of shivering thermogenesis. There is often a degree of amnesia/dysarthria/ataxia. The loss of coordination can make evacuation over rough ground problematical. In addition, although often normotensive, there is a degree of tachycardia and tachypnea.

Moderate hypothermia

In moderate hypothermia (28–32°C) the subject is often profoundly neurologically obtunded or even in a stupor. Shivering stops below 32°C and consequently inexperienced assessors can be misled into underestimating the severity of hypothermia. As the core temperature falls the subject becomes bradycardic and is at risk of developing atrial fibrillation. Blood pressure and respiratory rate falls and pupils become dilated (<30°C).

Severe hypothermia

When core temperature drops below 28°C, the subject becomes comatose and has absent corneal and oculocephalic reflexes. They are profoundly hypotensive and there is a high likelihood of developing ventricular fibrillation (maximum risk: 22°C); as core temperature falls they become

apneic, asystolic and areflexic with fixed pupils. The EEG is flat at 19°C.

Cardiac effects of hypothermia

There is an initial tachycardia, but cold has a negative inotropic effect causing decreased left ventricular contractility. There is a reduced effect of dopamine and noradrenalin, and increasing hypothermia is associated with dysrhythmias (atrial fibrillation T° < 32°C, ventricular fibrillation T° < 28°C, and finally asystole). There is a gradual development of bradycardia with a fall in heart rate of to approximately 50% of baseline at 28°C, and this is refractory to atropine.

Circulatory effects of hypothermia

In an attempt to preserve core temperature there is a peripheral vasoconstriction, which occurs early in the process. There is also an increase in blood viscosity and consequently there is an accumulation of metabolic waste products in poorly perfused tissues. Rewarming will re-perfuse these vascular beds causing possibly causing both local and central acidosis and cooling resulting in an afterdrop.

Respiratory effects of hypothermia

With cooling, there is respiratory depression, and an associated reduction in respiratory rate and tidal volume. There is approximately a 50% reduction in CO_2 production at 30°C. Bronchorrhea occurs, resulting in a risk of aspiration. There is inhibition of hypoxic pulmonary vasoconstriction which increases right to left shunts. This is associated with a left shift of HbO_2 curve and there is an increased risk of acute respiratory distress syndrome (ARDS).

Effects of hypothermia on the central nervous system

Hypothermia results in a 6–7% per °C drop in cerebral blood flow and there is a corresponding reduction in cerebral metabolism. Cerebal autoregulation is maintained until core temperature falls below 25°C. The electroencephalogram (EEG) becomes flat at 19°C and this is associated with an areflexic coma and unreactive mydriasis.

Metabolic effects of hypothermia

The metabolic rate also falls by approximately 6% per °C drop in T°C (i.e. 50% at T = 28°C) and oxygen consumption at 20°C is reduced to 25%. There is depressed liver function and a metabolic and respiratory acidosis. Initially there is hyperglycaemia. Hyperkalaemia from rhabdomyolysis can develop and there is adrenoceptor and baroceptor dysfunction.

Haematological effects of hypothermia

Haemoconcentration occurs in hypothermia, there is reversible platelet dysfunction and inhibition of clotting enzymes, and altered kinetics of plasminogen activator inhibitors (e.g. alpha 2 antiplasmin). This is an associated with an increased clotting time with deranged extrinsic pathway and DIC can develop.

Immunological effects of hypothermia

Mild hypothermia increases the incidence of wound infection. There is impairment of immune function, suppressed mitogen-induced activation of lymphocytes, and decreased production of interleukin-1b and interleukin-2. Thermoregulatory vasoconstriction is associated with increased risk infection.

Principles of treatment of hypothermia

The principles of treatment are first to prevent further heat loss and then to facilitate warming.

Passive rewarming

The principle of passive rewarming is to allow endogenous heat production to generate heat by shivering, an increase in metabolic rate, thyroid stimulating hormone (TSH), sympathetics. Fundamental is to reduce the heat loss by removing the individual from the cold environment, removing wet clothes and providing warm clothing/blankets.

Active rewarming

External heat sources are used to raise the core temperature. Hot drinks, heating blankets (fluid-filled), air blankets, radiant warmers, immersion in warm baths and hot water bottles/heating pads have all been used [114, 115]. Intracavity warming using warmed and humidified air, intraperitoneal, intra-vesicle and intra-pleural warming have all been described. In the profoundly hypothermic patient cardiopulmonary bypass is the safest approach.

Metabolic effects of rewarming

Oxygen consumption can increase by as much as 90%, and there will be an associated increase in carbon dioxide production (up to 60%). Occasional anaerobic metabolism will occur and rewarming rate of 0.5–2.0°C/h are recommended.

Concerns about the phenomenon called 'after drop' need to be borne in mind. This tends to occur with faster rewarming rates (1–2.5°C/h).

Practical aspects of the management of mild hypothermia

Once hypothermia has been recognised, the individual should stop climbing/walking and seek shelter. The exact shelter will depend on the situation and prevailing conditions. A mountain hut, tent, snow hole, bivi/bothy bag, cave or crevasse could all be used to get shelter from wind, snow, rain or other adverse conditions. Wet clothing should be removed and available warm and/or windproof clothing should be used to restrict heat loss. Insulate the individual from the ground to prevent further heat loss. If available, getting into a warm sleeping bag with a warm person can be helpful. It is important that others in the group are protected from further heat loss. Warm sugary fluids should be given by mouth.

Practical aspects of the management of severe hypothermia

Management of the profoundly hypothermic individual is considerably more challenging.

Profound hypothermia occurs with body temperatures below 28°C and there is depression of most physiological systems. While the asystolic, areflexic, apnoeic subject appears dead, hypothermia itself can have a protective effect on vital organs [116, 117] and full recovery may be possible even after hypothermic cardiac arrest [118, 119]. Victims should be transported as soon as possible to a centre where monitored rewarming is possible [120]. Appraisal of the exact situation, the evacuation options, the availability of communications systems to summon help and the timing to achieve evacuation all need to be considered. Where rapid evacuation by helicopter or motorised transport is possible this clearly simplifies the situation.

If there are likely to be significant delays in the evacuation then the individual should be warmed slowly and gently [121]. Sudden movements should be kept to a minimum in an attempt to reduce the risk of developing a cardiac arrhythmia. This is particularly important following immersion hypothermia [122]. The risk of ventricular fibrillation is maximal at 22°C. The victim may have concomitant injuries which caused the hypothermia (e.g. long bone or pelvic fractures, abdominal or head or chest injuries) which also have to be managed simultaneously (Figure 18.5).

The ability to treat severe hypothermia depends on a number of factors and should be directed to performing cardiopulmonary resuscitation (CPR) in cardiac arrest victims and transporting safely to a hospital setting where definitive rewarming can take place. Mouth-to-mask ventilation devices are most likely to fulfil the requirements of being safe, simple and efficient in the hands of a basic-trained rescuer [123]. However, individuals have been successfully resuscitated with core temperatures as low as 13.7°C with prolonged periods of CPR and long-term outcome is often very good [124]. Consequently the phrase 'No one is dead until they are warm and dead' has been used [125]. Interestingly, in patients who have been successfully resuscitated after cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia has been shown to increase the rate of a favourable neurological outcome and a reduced mortality [126]. The logical conclusion of this is to delay full rewarming, and it has recently been recommended that comatose patients after submersion, accidental hypothermia and cardiac arrest are treated with mild hypothermia for 12–24 hours [127] (Table 18.11).

Frostbite

Introduction

Frostbite has traditionally been considered a military problem, but is now becoming increasingly common in civilian populations. This in part reflects the growth in outdoor activities, and along with increased numbers of homeless, there has been a rise in frequency of cold exposure in the civilian population [128]. Consequently the management of cold injuries is important, not only for the rural physician in polar climates, but also for those who work in many urban hospitals. Frostbite injuries frequently affect those who are active and in the prime of their lives and can have disastrous long-term consequences. The spectrum of injury is enormous, varying from minimal tissue loss with mild long-term sequelae, to major necrosis of the lower limb with subsequent major amputations.

Thermoregulation is a balance between heat loss and heat production. When heat loss exceeds heat production, there is a net loss of heat and this will result in a fall in tissue temperature. Physiological responses to whole body cold exposure include peripheral vasoconstriction, resulting in increased intrinsic insulation, and increased metabolic rate, particularly shivering. Whole-body cooling or hypothermia is often associated with local freezing or non-freezing cold injury of peripheral tissues.

Frostbite occurs when the local temperature in an extremity falls low enough for ice crystals to form in superficial or deep tissues [128]. A number of factors will determine the severity of the frostbite injury, including environmental temperature, the wind chill factor and the length of exposure.

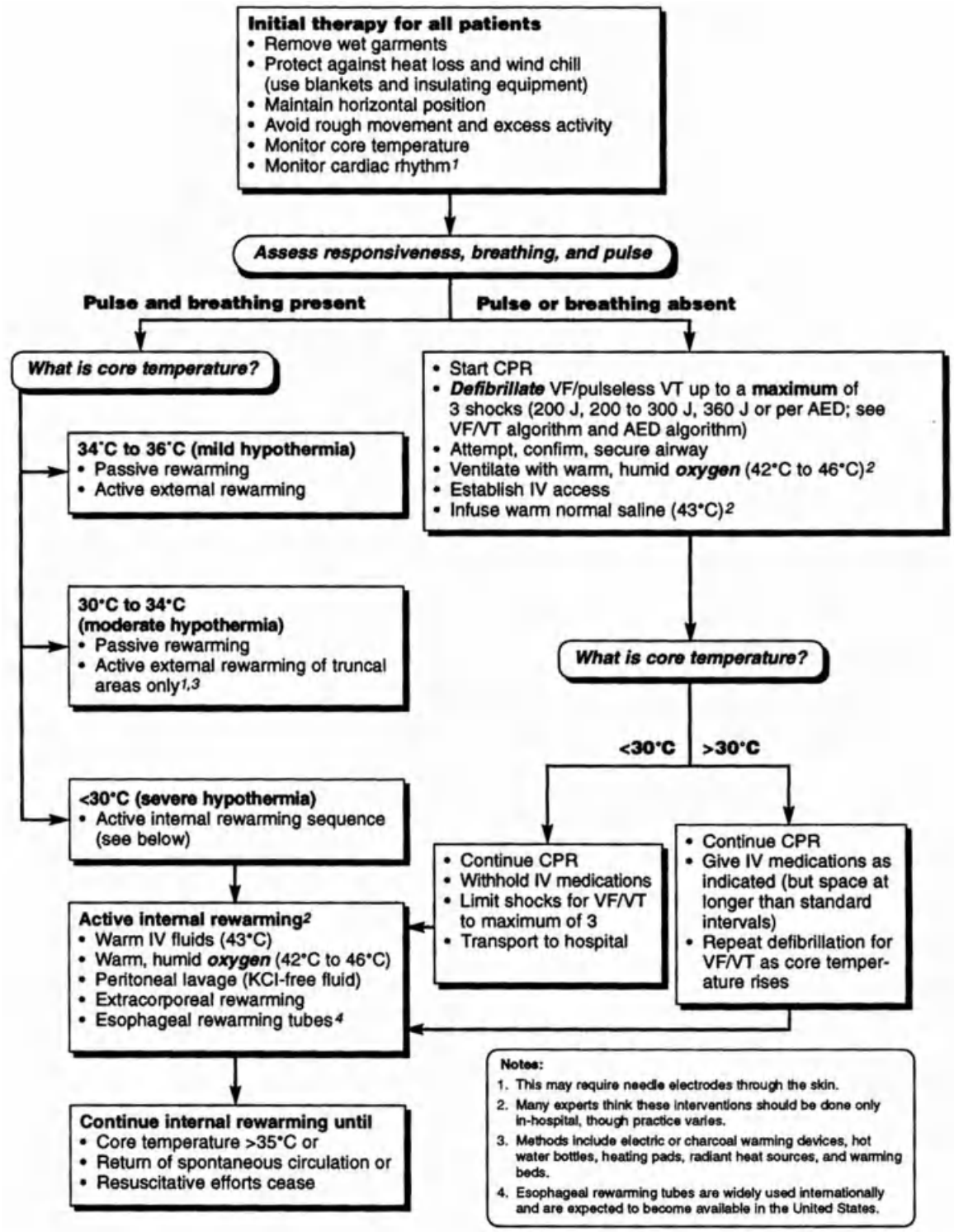

Figure 18.5 Management of hypothermia. Courtesy of PGMJ review.

Table 18.11 Recommended treatment for comatose patients after submersion, accidental hypothermia and cardiac arrest

Rescuers should follow state law and local standing orders. Generally, CPR should not be initiated if the patient:
- has been submerged in cold water for more than 1 hour
- has a core temperature of less than 50°F (10°C)
- has obvious fatal injuries, e.g. decapitation
- is frozen, e.g. ice formation in the airway
- has a chest wall that is so stiff that compressions are impossible
- rescuers are exhausted or in danger
- definitive care is not available within 3 hours.

Research into the pathophysiology of frostbite has revealed marked similarities with the inflammatory processes seen in burn injuries and ischaemia/reperfusion injury. Evidence for the role of thromboxanes and prostaglandins has resulted in a more active approach to the medical treatment of frostbite [128].

Epidemiology

A study into severe frostbite injuries in the northern Canada [129] found a number of predisposing factors, including alcohol consumption (46%), vehicle failure (19%), psychiatric illness (17%) and drug misuse (4%). Peripheral vasodilatation is accentuated by alcohol, and this, in combination with decision making, may in turn lead to a more severe injury. The need to amputate injured parts in most studies was closely correlated with the duration of cold exposure rather than the absolute temperature [130]. The feet and the hands account for 90% of injuries reported [131, 132]. Frostbite can also affect the face (nose, chin, earlobes, cheeks and lips), buttocks/perineum (from sitting on metal seats) and penis (joggers). Further risk factors for frostbite are listed in Table 18.12. Epidemiological studies suggest frostbite tends to affect mainly adults between the ages of 30 and 49 years [129, 131]. Scandinavians have used waterless ointments as an additional lipid layer to protect against frostbite. However, recent research suggests little protection is conferred [133].

Pathophysiology

The pathophysiological processes of frostbite have been studied using both human and animal models. It appears that local cold injury produces a series of changes that are divided into four phases: 'pre-freeze', 'freeze-thaw', 'vascular stasis' and 'progressive or late ischaemic' phase. There is overlap and the changes depend on factors such as the freezing rate, the duration of freezing, the extent of injury and thawing rate. Mills proposed a simpler scheme of frostbite injury [135] with only two phases: the cooling–supercooling–freezing stage; and a vascular stage that includes thawing (rewarming) and post-thaw.

Table 18.12 Factors that increase risk for frostbite [134]

Behavioural	Pathophysiological	Mechanical
Inadequate clothing and shelter	Genetic susceptibility	Tightly constrictive clothing (too many socks)
Inexperience	Dehydration and hypovolaemia	Contact with heat-conductive materials
Failure to respond appropriately to adverse conditions	High altitude, hypoxia and hypothermia	Rings on fingers
Alcohol and other drug use	Diabetes, atherosclerosis, vasculitis, arthritis	Immobility (military situations)
Psychiatric illness	Raynaud's phenomenon	Inadequate equipment
Smoking	Vasoconstrictive drugs	
	Cryoglobulinopathies	
	Sweating or hyperhydrosis (increased heat loss)	
	Previous frostbite	

Normal nerve function (and associated with this skin sensation) is lost around 10°C. As skin cools, cold-induced vasoconstriction is followed by cold-induced vasodilatation. This phenomenon, also known as the 'hunting response', protects extremities from cold injury (at the expense of heat loss). It occurs in 5- to 10-minute cycles. As the extremity cools further there will eventually be closure of the arteriovenous shunts, resulting in an avascular environment that protects the core from further heat loss [135]. With further cooling, blood become increasingly viscous, and microvascular constriction and transendothelial leakage of plasma occurs. With further cooling below 0°C, ice crystal formation occurs. Very low ambient temperatures, wind and moisture accelerate this rate.

Ice crystals tend to form initially in the extracellular fluid spaces. As a result of changes in extracellular osmotic pressure, free water is drawn across the cell membrane, in turn

causing intracellular dehydration and hyperosmolality. Consequently there are extra- and intracellular electrolyte and pH changes, dehydration and destruction of enzymes. Cell membranes are damaged and microvascular function is compromised, with the endothelium separating from the arterial wall lamina. There is resultant ultrastructural capillary damage, loss of mitochondria in muscle cells and other intracellular damage [136].

Blebs or blisters may form as a result of vasodilatation, oedema, stasis and coagulation, and platelet, fibrin and erythrocyte aggregates obstruct the vessels. As in burns, reperfusion injury occurs, and there may be increased compartment pressures. Oxygen-free radicals, neutrophil activation and other inflammatory changes also appear to be implicated. Prostaglandin $F_{2\acute{\alpha}}$ ($PGF_{2\acute{\alpha}}$) and thromboxane A_2 (TXA_2) cause platelet aggregation and thrombosis, which results in ischaemia and, interestingly, Robson and Heggers found markedly elevated levels of $PGF_{2\acute{\alpha}}$ and TXA_2 in frostbite blister fluid [137]. These eicosanoid derivatives have been implicated as mediators of progressive dermal ischaemia in burns, frostbite and ischaemia/reperfusion injuries [138].

Following the initial injury, either vascular recovery with dissolution of clots occurs, or vascular collapse, which results in thrombosis, ischaemia, necrosis and gangrene. Refreezing after thawing causes intracellular ice formation with extensive cell destruction and further release of prothrombotic, vasoconstrictive $PGF_{2\acute{\alpha}}$ and TXA_2. A rabbit ear model demonstrated increased tissue survival after a blockade of the arachidonic acid cascade at all levels [138]. The most marked tissue salvage resulted when specific TXA_2 inhibitors were used. This has now been shown to be effective in clinically [139].

Clinical presentation

Initially, most people describe the affected extremity as feeling cold to the touch and they will often complain that it feels clumsy, 'like a block of wood'. The cold numbness is associated with an accompanying sensory loss [132].

Thawing and reperfusion is often accompanied by an intense throbbing pain, which may persist for weeks or months, even after tissue demarcation. Residual tingling sensation is probably due to an ischaemic neuritis [130, 140]. The subsequent clinical course is variable, but usually frostbite victims experience some degree of sensory loss for 4 or more years after injury, perhaps indefinitely [130].

The initial appearance of frostbite may be deceptively benign, but frozen tissue may appear mottled blue, violacious, yellowish-white or waxy. Following rapid rewarming, there is an initial hyperaemia, even in severe cases [141].

Favourable prognostic signs include retained sensation, normal skin colour and clear rather than cloudy fluid in any blisters present. Early formation of oedema and clear blisters that extend to the tips of the digits are a good sign. Poor prognostic signs include non-blanching cyanosis, firm skin, lack of oedema and small, proximal, dark haemorrhagic vesicles (indicates damage to the subdermal vascular plexus) [131]. However, no prognostic features are entirely predictive and weeks or months may pass before the demarcation between viable and non-viable tissue becomes clear.

Frostnip

Frostnip is a very early stage of frostbite. If the cold extremity is rapidly warmed it should return to normal within 30 minutes and there should not be any long-term damage.

Frostbite classsification

Frostbite can be divided into either mild or superficial (no tissue loss) and severe or deep (with loss of tissue) [130, 141, 142] (Table 18.13). In 2001 Cauchy *et al.* [143] recognised that frostbite classifications were based on

Table 18.13 Classification of cold injury according to severity [134]

Superficial	Deep
1st degree	*3rd degree*
Partial skin freezing	Full-thickness skin and subcutaneous freezing
Erythema, oedema and hyperaemia	Violaceous/haemorrhagic blisters
No blisters or necrosis	Skin necrosis
Occasional skin desquamation (5–10 days later)	Blue-grey discolouration
2nd degree	*4th degree*
Full-thickness skin freezing	Full thickness skin, subcutaneous tissue, muscle, tendon and bone freezing
Erythema, substantial oedema	Little oedema
Vesicles with clear fluid	Initially mottled, deep red or cyanotic
Blisters, desquamation and black eschar formed	Eventually dry, black and mummified

retrospective diagnoses and could not predict the extent of final tissue loss and prognosis for the patient. They proposed a new classification system that begins at day 0 (just after rewarming) and is based mainly on the topography of the lesion and on early triple-phase bone scanning (using ^{99}technetium) [144]. This is a very useful classification for both doctor and patient, since it allows accurate determination at a very early stage of the likely extent of subsequent tissues loss and early coverage of ischaemic bony structures [134, 145]. Magnetic resonance imaging or magnetic resonance angiography (MRI/MRA) [146] has also been used as an alternative.

Treatment

Pre-thaw field care phase [147]

If caught out in the field and there is a possibility of onset of frostbite one should move out of the wind and seek shelter. One should drink warm fluids, remove boots (consider problems with replacement if swelling occurs), remove wet gloves and socks and replace with dry ones, warm the cold extremity by placing in a companion's armpit or groin for 10 minutes only, replace boots, and take aspirin (75 mg) for its antiplatelet effect and ibuprofen (800 mg) for its antiprostaglandin effect. Do not rub the affected part or apply direct heat. If sensation returns, one can continue to walk. If there is no return of sensation, go to the nearest warm shelter (hut or base camp) and seek medical treatment. If at altitudes over 4000 m, consider supplementary oxygen.

Field rewarming should only be attempted if there is no further risk of refreezing [130]. Tissue that is thawed and then refrozen almost always dies. Consequently, the decision to thaw the frostbitten tissue in the field commits the provider to a course of action that may involve pain control, maintaining warm water baths at a constant temperature, and protecting tissue from further injury during rewarming and eventual transport. Once rewarmed in the field, frostbitten extremities cannot be used for ambulation.

Immediate hospital care

The standard approach to the initial treatment of frostbite is the strategy originally outlined by McCauley and Heggers [148] (*see* Table 18.14). Hypothermia and concomitant injury should be evaluated first. Systemic hypothermia should be corrected to a core temperature of 34°C before frostbite management is attempted [130]. Rewarming should be carried out in a whirlpool (recirculating water) with a mild antibacterial agent (povidone-iodine or chlorhexidine).

Table 18.14 Treatment protocol for frostbite (modified from McCauley and Heggers [148]

1 Admit frostbite patient to specialist unit if possible
2 Evaluate for hypothermia, concomitant injury or complicating problems
3 On admission, rapidly rewarm the affected areas in warm water at 37–39°C (99–102°F) for 15–30 min or until thawing is complete
4 Debride clear or white blisters and apply topical aloe vera (Dermaide aloe) every 6 h
5 Leave haemorrhagic blisters intact and apply topical aloe vera every 6 h
6 Splint and elevate the extremity
7 Administer anti-tetanus prophylaxis (toxoid or immunoglobulin (Ig))
8 Analgesia: opiate (intravenously or intramuscularly) as indicated
9 Administer ibuprofen 400 mg orally every 12 h
10 Administer benzyl penicillin 500,000 U every 6 h for 48–72 h
11 Administer daily hydrotherapy in 40°C water for 30–45 min. Do not towel dry affected tissue
12 Prohibit smoking

The State of Alaska Cold-injury Guidelines recommend a lower-temperature waterbath of 37–39°C, which decreases the pain for the patient while only slightly slowing rewarming [149]. The time period recommended for rewarming varies from 15 to 30 minutes [148] up to 1 hour [147]. Rewarming should continue until a red/purple colour appears and the extremity becomes pliable. Active motion during the rewarming period is beneficial but care should be taken to prevent the extremity from touching the sides of the whirlpool. Intravenous fluid resuscitation is not usually required for frostbite. If the patient has been at altitude then it is more likely that they are dehydrated; moreover, if they are also hypothermic they may exhibit a cold diuresis, due to suppression of antidiuretic hormone. This often requires correction with intravenous fluids.

Post-thaw care

Blisters containing clear or milky fluid should be debrided and covered in aloe vera, a potent anti-prostglandin agent, every 6 hours. Splinting, elevating and wrapping the affected part in a loose, protective dressing should follow the administration of the aloe cream. Padding should be put between the patients' toes if affected. Haemorrhagic blisters should be left intact to prevent desiccation of the underlying tissue.

If they restrict movement they can be drained with their roofs left on. Tetanus toxoid, opiate analgesia and ibuprofen are all indicated. Ibuprofen (400 mg po, every 12 hours) [130] is useful as it provides systemic anti-prostaglandin activity that limits the cascade of inflammatory damage. Aspirin is less beneficial as it prolongs blockade of all prostaglandin synthesis, including some prostacyclins that are beneficial for wound healing. The role of clopidogrel in frostbite has yet to be assessed.

When the skin is oedematous, penicillin is administered as oedema inhibits the skin's own streptococcoidal properties [128]. If there are further signs of infection, further antibiotic use is indicated. Almost all patients should be admitted to hospital and given that alcohol intoxication, psychiatric illness and homelessness are common features of the frostbite patient, immediate discharge is rarely prudent.

Goals of hospital treatment include keeping the patient quiet, well nourished, well hydrated and pain free. Wound care must be meticulous and further trauma must be avoided. Injured extremities should be elevated to avoid oedema. Physiotherapy is important and the patient should be encouraged to mobilise as soon as possible [130]. Extremities are treated with clean, dry dressings and twice-daily whirlpool baths with added chlorhexidine. This encourages the eschars from the blisters to separate from the underlying healthy tissue.

Surgery

There is rarely any urgency to intervene surgically, and if necessary, it should be undertaken by a surgeon with appropriate experience usually 6–12 weeks after the injury. The exceptions to this being fasciotomy for compartment syndrome and occasionally early amputation is indicated if liquefaction, moist gangrene, or overwhelming infection and sepsis develops. In the vast majority of cases it is the failure to delay surgery that is a major source of avoidable morbidity. The functional end result of any surgery needs to be considered, and ideally where major limb loss is foreseen the early involvement of a multidisciplinary rehabilitation team. However, some clinicians are now advocating a more aggressive approach. The recent introduction of ^{99}technetium scintigraphy [134, 143, 145] and MRI scanning [146]allows very early assessment of tissue viability which enables early planning of interventions.

Adjunctive therapies

Hyperbaric oxygen therapy (HBO) increases the deformability of erythrocytes, diminishes oedema formation in burned and post-ischaemic tissues, and has a bacteriostatic effect [150]; it also may act as an antioxidant [151]. The role of HBO therapy in frostbite has had mixed acceptance among authors. Several animal studies have demonstrated it to be of no benefit [18], yet two recent studies in humans have yielded excellent results [150, 151].

Sympathectomy

Sympathectomy may have a role in preventing some long-term sequelae of frostbite such as pain (often due to vasospasm), paresthesias and hyperhidrosis [152]. Early sympathectomy, performed within the first few hours of injury, is said to increase oedema formation and leads to increased tissue destruction. However, if performed 24 to 48 hours after thawing it is thought to hasten resolution of oedema and decrease tissue loss [152]. However, since a sympathectomy is irreversible, great caution should be exercised when considering its use, particularly since the advent of alternative intravenous vasodilators, and some would argue there is now no role for its use in frostbite .

Vasodilators

Iloprost is an intravenous prostacyclin analogue that has profound vasodilatory properties and has been used with some success [130]. It is used in arterial surgery to mimic the effect of a sympathectomy. Intra-arterial reserpine has been used in frostbite to prevent vasospasm. The use of pentoxifylline [153], a methyl-xanthine-derived phosphodiesterase inhibitor, has yielded some promising results in human trials. It increases blood flow to the affected extremity, decreases platelet hyperactivity and helps normalise the prostacyclin to TXA_2 ratio. It has been clinically proven to enhance tissue survival. The alpha-blocker buflomedil has been used to increase peripheral blood flow [143].

tPA

A small study assessing the effectiveness of tissue plasminogen activator (tPA) in reducing amputation rates in frostbite has recently been reported [154]. Among the six patients who received tPA within 24 hours of injury, six of 59 (10%) affected fingers or toes were amputated, compared with 97 of 234 (41%) among those who did not receive tPA. It is postulated that rapid clearance of the microvasculature improves tissue salvage.

Long-term sequelae

The long-term sequelae of frostbite have not been well studied. The functional use of extremities following a partial amputation is variable and injury-specific. Partial foot

amputations radically alter the biomechanics of the foot, and this, combined with frostbite-induced neuropathy, means specialist custom-made footwear is required to maximise the functional result and minimise secondary injuries. Tissue that has recovered from frostbite is more susceptible to further injury and this needs to born in mind when advising individuals about a return to environments where they may be at risk. Preventative measures remain the mainstay to primary and secondary treatment. Major lower limb amputations, while rare, are occasionally necessary, and appropriate multidisciplinary care is essential [155].

Internet

Using the internet, a virtual opinion on a patient affected by frostbite, hypothermia or altitude can be sought from anywhere in the world [156]. The UK-based service can be accessed via the Diploma in Mountain Medicine or the British Mountaineering Council websites. The service is run by diploma faculty members and is being increasingly used by climbers and physicians worldwide, often to obtain a second opinion or to seeking more specialised advice. It is also possible to follow-up patients in a 'virtual clinic', reviewing recent digital images and discussing management options either by phone or via email.

Non-freezing cold injuries

Individuals exposed to a cold wet environment for long periods of time are at risk of developing a non-freezing cold injury (NFCI). The condition is often unreported or undiagnosed so its true prevalence is difficult to assess. Rewarming after sustained exposure to non-freezing conditions reveals a localised sensory neuropathy. Rewarming results in a short period of pale cyanosis, followed by hyperaemia, with redness, swelling, full pulses and pain [157].

Pain is more prolonged than that experienced in freezing cold injury, and is the most common reason for presentation. The final phase can last for months or years and is associated with an increased sensitivity to cold. There are often surprisingly few objective clinical signs.

Infra-red thermography (NIT) can be used to assess the affected individual's response to a standard cold stress. NIT may be helpful in confirming the diagnosis, assessing the severity of the injury and finally monitoring the recovery or otherwise from the NFCI [158]. There is variability in some individuals' response to the standard NIT test and consequently interest is being shown in the use of gentle exercise prior to the cold sensitivity test [159].

NFCI ranges from mild to severe. There is often persisting oedema and hyperhidrosis, making the individual susceptible to fungal infections, and chronic pain resembling causalgia or reflex sympathetic dystrophy is reported. In severe cases the cold sensitisation is sufficiently bad to mean that individuals are unable to work outside. The profound sensory neuropathic foot can develop ulceration, tissue loss ultimately resulting in either minor or major lower limb amputation. Ongoing care within a specialist foot clinic using custom-made shoes and insoles appear to improve functional outcome. Multidisciplinary team approaches such as healing of the ulcerated neuropathic foot using patella-bearing orthoses has been described [160].

NFCI pain is often so severe as to require tricyclic antidepressants, and this should be instituted at an early stage. Failure to do so increases the risk of developing severe chronic pain resistant to all subsequent treatment modalities. Early involvement of pain specialists is important. Sympathectomy usually results in longer-term deterioration. It is thus essential to control pain following NFCI at the earliest opportunity. Unlike freezing cold injury, NFCI should be allowed to rewarm slowly. Management should then follow the standard conservative protocol employed in freezing injury.

With the likelihood of chronic sequelae and only limited potential for treatment, the most effective approach to NFCI is to try to prevent its occurrence. There is a need to raise awareness to those most susceptible, particularly, for example, junior military recruits. Although almost all cases of NFCI involve the feet, as many as 25% may also have injured hands. Afro-Caribbeans appear to have a significantly increased susceptibility to NFCI as well as freezing cold injury [161]. This may be a result of an impaired or reduced cold-induced vasodilatory response in Afro-Caribbeans compared with Caucasians [162]. These ethnic differences remain when Afro-Caribbeans move to colder areas.

Sunburn

One of the characteristic features of the polar and mountain environment is the huge variation in climactic, thermal and environmental conditions. Excessive exposure to UV light can result in severe sunburn. The level of ultraviolet radiation is affected by sun elevation (highest at midday), latitude (reduced towards the poles), cloud cover (90% penetration of light cloud by UV), altitude (10–12% increase in UV for every 1,000 m of height gain), ozone and ground reflectance (clean snow reflects up to 80% of UV light). Avoidance of exposure, protective clothing and powerful sunscreens are required. Individual susceptibility is

important as is an awareness of the risk, particularly in windy cloudy conditions.

Most cases of sunburn can be treated with simple analgesia (paracetamol and NSAIDs). Topical steroids are thought by some to be helpful [163]. Oral rehydration is usually adequate and blister formation can be treated with good nursing care with antibiotics if the risk of secondary infection is thought to warrant them.

Snow blindness

Increased UV light exposure to the cornea and conjunctiva exacerbated by snow reflectance and being at altitude can result in snow blindness or photo-opthalmia. This can range in severity from mild to severe. Approximately 4 hours after exposure there is a feeling of grittiness in the eye, and this gradually develops into severe pain, headache, papillary vasoconstriction and spasm of the eyelids. On examination there is often peri-orbital oedema and conjunctival inflammation and this lasts for 6-10 hours and resolves over 48–72 hours. Treatment consists of oral and local analgesia, cold compresses, topical steroids and topical antibiotics, with an eye patch to exclude light and secondary damage.

In a dangerous mountain or polar environment, evacuation of the affected individual can be difficult. Prevention is clearly important and consists of having and wearing (even in flat light conditions) appropriate protective sunglasses/goggles. Carrying a spare pair when moving above the snowline is to be strongly recommended.

Dehydration

At high altitude and when exercising hard in polar regions, hyperventilation and sweating can result in dehydration which can adversely affect performance and so safety. With temperatures below freezing there is no easy access to water. Preparation by melting adequate snow for the day, before leaving tents or snow holes (>2–4 litres/person), and the use of appropriately robust and insulated containers is important. The popular 'CamelBac' drinking systems suitable for temperate climates tend to freeze, particularly in the exposed tubing system. Even insulated bottles will freeze in rucksacks when temperatures are below −25 to −30°C, and in such circumstances drinks are best kept close to the body.

Carbon monoxide poisoning

Carbon monoxide is a colourless, odourless gas produced by incomplete combustion of carbon-based fuels. It has an affinity for haemoglobin that is 200 times stronger than oxygen. Cooking in a poorly ventilated tent, snow hole or hut can lead to a build-up of the gas in less than 30 minutes. Symptoms are often rather non-specific and not dissimilar to acute mountain sickness, but include headache, nausea and dizziness. Paraesthesia, chest pain and loss of conciousness are late signs. Although rare it is an avoidable cause of death and adequate ventilation is essential.

DIVING MEDICINE

Introduction

Recreational diving is popular worldwide. The lure of colourful tropical reefs and warm water attracts travellers to a variety of diving holiday destinations. Previously inaccessible environments such as the Arctic and Antarctic can now be reached with relative ease (Figure 18.6), and the increase in adventure tourism enables travel to ever more remote locations. Self-contained underwater breathing apparatus (SCUBA) allows the diver freedom to explore oceans, riverbeds, lakes or flooded cave systems. Scientific and archaeological underwater expeditions draw volunteer divers and diving medical staff to distant sites, and advances in technical diving can greatly extend the depth and time available for underwater exploration for more adventurous divers.

The underwater world has inherent risks for humans. Pressure effects on gases during or after a dive may cause

Figure 18.6 Diver under ice.

Table 18.15 Medical problems associated with scuba diving

Illness related to environment	Illness related to diving
Drowning/Near drowning	Nitrogen narcosis
Hypothermia	Carbon dioxide excess
Heat stroke, sunburn	Oxygen toxicity
Sea-sickness	Carbon monoxide poisoning
Otitis externa (swimmer's ear)	Barotrauma, arterial gas embolism
Marine envenomation	Decompression sickness
Dangerous marine life	
Waterborne infectious diseases	
Trauma	

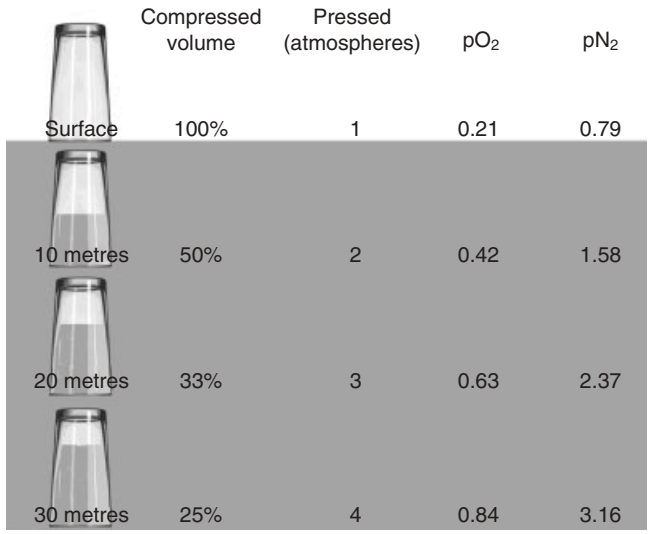

Figure 18.7 The effect of depth on gas volume and partial pressures.

illness or injuries. Remote locations may not themselves increase this risk, but the time taken to reach specialist treatment, in particular to recompression facilities, is often significantly longer. An understanding of the background physics and physiology that mark diving-related illness as different to many other illnesses is useful for those doctors involved in assessment of fitness to dive, treating divers abroad or in contact with divers returning from holiday. Expedition medical officers require a working casevac plan for any diver requiring recompression.

Divers are exposed to environmental problems, such as drowning, hypothermia or marine envenomation as well as those directly caused by diving (Table 18.15). Special considerations need to be given to diving at altitude, and in extremely hot or cold climates where the environment can stress the equipment as well as the individual.

Travellers wishing to dive abroad must be aware of maximum depth limits to SCUBA diving imposed by their medical insurance; their insurance will be invalidated if an accident occurs while diving outside these limits. The government of some countries may also impose legal limits – for example, the government of the Maldives enforces a 30 metre depth limit on all dives, with total dive duration of 60 minutes maximum. Despite these conservative limits, there are more than 40 cases of decompression sickness in the Maldives each year.

Diving physics

Underwater, a recreational diver breathes from specially designed equipment – scuba – consisting of a gas-filled cylinder and a means to regulate the flow of gas to the diver. Compressed air is commonly the breathing gas (and used for simplification throughout this chapter), but other gases may be used, providing differing concentrations of oxygen, nitrogen or helium depending on the depth and the diver's requirement.

At the water's surface the pressure is one atmosphere absolute (one ATA, 100 kPa or 1 bar). As a diver descends during a dive, there is a linear increase in pressure due to the weight of water above the diver, and this is transmitted over the entire body. For each 10 metres of vertical descent, the pressure increases by one atmosphere (Figure 18.7). Most of the body is non-compressible, but gas is easily compressible according to Boyle's Law (Table 18.16). Pressure changes are greatest close to the surface, so that an upturned glass of air filled at the surface will contain only half the volume of air at 10 metres [164]. Gas-filled spaces such as the middle ears, sinuses or lungs will be compressed during descent, and expand on ascent, unless equalised with the surrounding pressure.

Standard diving equipment includes a high-pressure cylinder of breathing air at 200–300 atmospheres (bar) when full. The pressure is reduced by a two-stage regulator to deliver air on demand to the diver at a pressure equal to that of the surrounding water. Human lungs cannot tolerate pressure differences beyond a few centimetres of water.

The composition of air is approximately 79% nitrogen and 21% oxygen, so the partial pressures at one atmosphere are 0.79 and 0.21 respectively (Dalton's Law, Table 18.16). Density and partial pressure increase in a linear manner as depth increases, so that at 20 metres, the partial pressures (and density) are three times that at the surface, with three times as many molecules in each breath (Figure 18.7). Therefore a large concentration gradient exists, particularly at the start of the dive, for oxygen and nitrogen to pass from the

alveoli to dissolve in blood and body tissue (Henry's Law, Table 18.16). Different tissues absorb nitrogen at slower or faster rates depending on their blood flow and tissue solubility. The increased partial pressures of nitrogen and oxygen at depth can cause nitrogen narcosis and oxygen toxicity respectively. Other gases may also become toxic (e.g. contaminants such as carbon monoxide) [165].

When a diver ascends towards the surface, the concentration gradient will be in the opposite direction and absorbed molecules need to pass out of the body. Excess oxygen can be metabolised, but inert gases such as nitrogen can cause problems during or after ascent if the pressure is lowered too quickly. As the partial pressure becomes lower in the air breathed, the partial pressure of nitrogen in blood and tissues exceeds that of the ambient pressure. This can result in bubble formation, leading to the collection of symptoms known as decompression sickness (DCS).

Table 18.16 Gas laws and diving

Gas law	Clinical implication
Boyles Law The volume of a fixed mass of gas is inversely proportional to the pressure at a constant temperature	Barotrauma of descent, e.g. mask, ear, sinus 'squeeze' Barotrauma of ascent, e.g. pulmonary barotrauma, arterial gas embolism (AGE)
Dalton's Law The pressure of a single gas in a mixture of gases is known as the 'partial pressure'	Breathing gas composition Carbon monoxide contamination and poisoning
Henry's Law The amount of gas that will dissolve in a liquid is proportional to the partial pressure of the gas over the liquid, at a constant temperature	Nitrogen (or other inert gas) absorption Nitrogen narcosis at depth Nitrogen bubbles during or after ascent

Conduct of diving

A simplified standard dive profile is shown in Figure 18.8. The length of time a diver can stay at any given depth is determined by the use of decompression tables or dive computers. These provide the diver with information on the maximum time at depth (maximum bottom time) and ascent rates. They also provide information on the minimum time between dives, based on the planned depth of a second (termed 'repetitive') dive. Dives may be within 'no-decompression limits' whereby a diver can ascend directly to the surface, at the advised ascent rate, at any time during the dive. Longer or deeper dives require 'decompression stops' during ascent, in which a diver must control their buoyancy at a given depth and remain at that depth for a specified duration to allow nitrogen elimination, before continuing the ascent towards the surface. Failure to perform decompression stops will put the diver at increased risk of DCS.

It may take several hours for all the absorbed nitrogen to be eliminated from the body. If a diver undertakes a second dive within a short surface interval, further nitrogen is absorbed into tissues that are already partially saturated. Decompression tables and computers attempt to take this 'residual nitrogen' into account, but any error in the prediction will be multiplied with successive dives. Travel that results in a decrease in atmospheric pressure after a dive – for example crossing a mountain range or flying – will increase bubble formation.

Water conducts heat away from the body about 20 times more rapidly than air. Immersion, particularly in cold water,

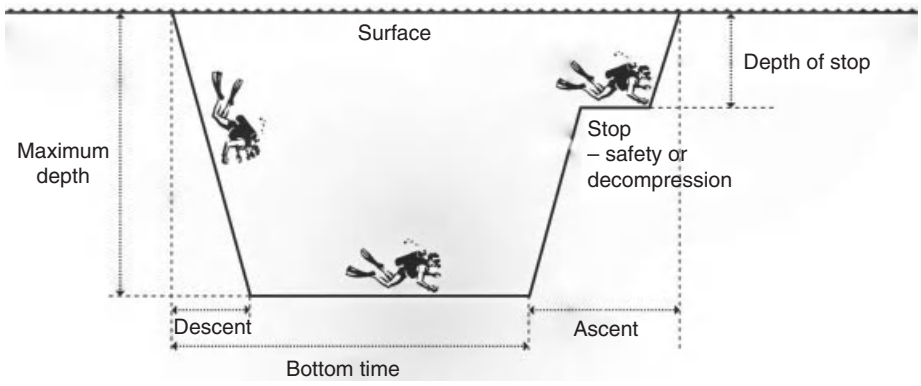

Figure 18.8 Simplified single dive profile.

causes peripheral vasoconstriction and a cold-induced diuresis. Breathing dry cylinder air through the mouth leads to further water loss. Divers are often in a state of relative hypovolaemia at the end of a dive. Dehydration due to heat, gastrointestinal upset or excess alcohol consumption compounds any dehydration [166].

Illness caused by diving

Decompression illness

There is often confusion in the use of terminology used to describe medical conditions related to diving. Some definitions are given here.

- **Decompression illness (DCI)** is a term used to describe any symptoms occurring after a dive that are related to bubble formation. DCI therefore encompasses both decompression sickness and arterial gas embolism.
- **Decompression sickness (DCS)** describes symptoms due to bubble formation from dissolved inert gas in tissues or blood.
- **Arterial gas embolism (AGE)** (see below) is due to bubbles occurring in arterial blood following pulmonary barotrauma. When the brain is affected by these bubbles, the term 'cerebral arterial gas embolism (CAGE) is used.

There is an area of overlap between these conditions, as a diver who has been at depth for some time will have absorbed nitrogen molecules into tissues. A rapid ascent may cause pulmonary barotraumas, leading to AGE. The high concentration of nitrogen in the tissues will also come out of solution; this may form bubbles causing separate symptoms or increase the size of bubbles due to AGE, thus worsening symptoms and prognosis.

Decompression sickness

Pathophysiology

At sea level (one atmosphere) our body tissues are in a state of 'saturation' of oxygen and nitrogen, containing the same gas partial pressures as air. Descent under water on SCUBA increases alveolar partial pressures such that nitrogen (and oxygen) move into the tissues.

Certain tissues absorb nitrogen more quickly than others, and these are known as 'fast tissues'. Fast tissues tend to have a good blood supply and low fat content, e.g. muscle or brain, and can become fully saturated with nitrogen within the period of a recreational dive. Tissues that take up nitrogen more slowly tend to be fatty tissues or tissues with poor blood supply, such as tendons. These are known as 'slow tissues'. At the end of a dive different tissues are at different stages of nitrogen saturation.

Nitrogen elimination depends on the blood flow to the tissue, and on the rate of ascent (rate of decrease in pressure) leading to a concentration gradient from tissues to blood to alveoli. Transport out of the tissues takes time, and the fall in tissue nitrogen pressure may lag behind the fall in alveolar nitrogen partial pressure. This can lead to the condition of 'supersaturation' in tissues, forming microbubbles as the nitrogen comes out of solution – often likened to releasing the top of a bottle of fizzy drink. These bubbles themselves can further slow nitrogen elimination.

Bubbles are now thought to form during or after most dives, but are not always associated with symptoms of decompression sickness. Venous bubbles can be detected using Doppler ultrasound on decompression stops, safety stops or within minutes of surfacing. Cold limbs, heavy exercise during or after a dive, or damaged tissue due to a previous injury may affect nitrogen uptake and elimination and increase bubble formation. Many other factors in an individual and conduct of diving affect the likelihood of DCS (Table 18.17).

Nitrogen bubbles cause damage by:

- obstruction to blood flow (important in spinal cord or brain)
- blood vessel endothelial damage, activation of leukocytes and platelets
- bubble growth (small bubbles empty into larger ones)

Table 18.17 Factors predisposing to decompression sickness

Factor
Dive profile
Close to depth/time limit
Depth greater than 30 metres
Omitted decompression
Repetitive diving, particularly over several days
Rapid ascent
Multiple ascents and descents during a dive
Exercise after dive
Coincidental illness
Ascent to altitude or flying soon after diving
Poor physical fitness
Increasing age
Obesity
Dehydration
Physical injury
Hypothermia
Patent foramen ovale (large)

Table 18.18 Symptoms of decompression sickness

Musculoskeletal	*Neurological*
• Joint pain	• General malaise or fatigue
	• Impaired cognition
Skin	• Paraesthesia (pins and needles)
• Pruritis, rash, swelling	• Weakness
	• Paralysis
Cardiorespiratory	• Sensory loss
• Chest pain or tightness	• Loss of balance, loss of coordination
• Dyspnoea	• Urinary retention
• Haemoptysis	• Visual disturbance
	• Coma

• mechanical distortion of tissue,
• activation of inflammatory pathways – complement, kinnin, coagulation and fibrinolytic pathways

Symptoms

These are variable and are usually divided into Type 1 (mild) or Type 2 (serious) symptoms. Type 1 DCS symptoms include joint pain (often knee of shoulder) without tenderness, or an itchy erythematous marbled skin rash (cutis marmorata). Type 2 includes cardiorespiratory or neurological symptoms (Table 18.18). Patients presenting with rapidly deteriorating neurology or cardiorespiratory symptoms, particularly if combined with CAGE, have a high mortality rate (known as Type 3 DCS).

Divers often present following considerable delay after the onset of symptoms. Symptoms may be vague and joint pain is often attributed to musculoskeletal strain. There is also evidence that divers deny that they have symptoms due to DCS, which may be due to cerebral involvement. Onset of symptoms may occur during a flight back from a diving holiday, due to the reduction in atmospheric pressure.

Treatment

1 First aid, standard ABC, lay the diver on a flat surface.
2 Oxygen should be provided as quickly as possible and continued during transport to a recompression facility. Oxygen provides a diffusion gradient for nitrogen out of the body, and increases oxygen delivery to ischaemic tissues.
3 Baseline clinical examination, including neurological examination.
4 Fluid therapy – oral or intravenous depending on diver's condition.
5 Recompression treatment.
6 Remember the diver's buddy who has usually dived a similar profile and may also require treatment.
7 Review clinical examination.

Neurological examination

A rapid neurological examination will quickly determine serious neurology and provide a baseline for the progress of symptoms. Weakness, sensory deficit and loss of balance are important findings.

Progress of symptoms

It is not uncommon for there to be full or partial improvement of symptoms on oxygen at the surface when treating a diver for either DCS or CAGE. Unfortunately, this improvement is not always sustained, and recurrent symptoms are frequently less responsive to recompression treatment. It is imperative that transfer, on oxygen, to a hyperbaric treatment centre is not delayed or stopped due to symptom improvement.

Recompression

Recompression is the definitive treatment for all types of DCS. The diver is compressed in a hyperbaric chamber breathing 100% oxygen via a face mask. The presumed mechanism of action is that bubbles are compressed to a smaller size, or back into solution, and nitrogen excretion is enhanced by breathing oxygen. There are several treatment protocols, but the most common is recompression to 18 metres initially, reducing to 9 metres after a period determined by symptom improvement or relief [167]. The diver breathes 100% oxygen, but has several breaks on air, to reduce the risk of oxygen toxicity. During these air breaks the diver can be re-examined to determine any improvement [168].

Adjunct therapy

In addition to recompression, various adjunct therapies are currently being investigated. Non-steroidal anti-inflammatory agents have analgesic action and also inhibit the inflammatory cascade. Faster resolution of symptoms can be obtained, but the outcome is no different [169]. Aspirin is not recommended as its anti-platelet action may increase bleeding in spinal cord DCS. Lignocaine has been shown to reduce cognitive impairment due to circulatory microbubbles following cardiac bypass surgery [170]. Case reports

suggest benefit when used in CAGE, although its use in DCS is unclear.

Prevention

It is now known that intravascular bubbles are formed following many dives, even those well within decompression table or computer algorithm limits. There remains uncertainty over many factors leading to DCS, but bubble formation can be reduced by diving conservatively, minimising the number of repetitive dives within a day, and having a break from diving (e.g. day off) during a prolonged period of diving. Venous bubble formation has been shown to be reduced significantly when a safety stop is performed on ascent at between 3 and 6 metres for a period of 3–5 minutes.

Outcome of DCS

Full recovery is more likely with early recognition and prompt treatment. Serious symptoms may not always respond to recompression, and there may be persistent neurological sequaelae, such as weakness, paralysis, loss of coordination, loss of bladder control or loss of higher cerebral functions. Death is rare, but more likely when DCS is combined with CAGE.

Following treatment for DCS, the diver will be advised on the time period that he should refrain from diving.

Patent foramen ovale

A patent foramen ovale (PFO) is an opening in the heart between the left and right atria, which usually closes after birth. In about 30% of the population a PFO can be pushed open by a probe at post-mortem (probe-patent) and these are probably functionally irrelevant. Larger PFOs (around 0.5–1 cm in size) can act as a conduit for bubbles passing between the right (venous) and left (arterial) circulation, bypassing the lungs, which normally filter bubbles. Bubbles then enter the arterial circulation and pass as emboli to organs, causing damage, particularly in areas of poor blood supply [170].

A large PFO is associated with rapid-onset neurological, cardiovascular and skin DCS (occurring within 30 minutes of surfacing). The risk of DCS is related to the size of the shunt and for large PFOs the risk is increased by five, from 1 in 20,000 dives to 1 in 4,000 dives. However, this risk does not currently justify routine screening prior to diving. Following an incident of DCS, particularly of rapid onset, divers are often advised to be screened using bubble contrast echocardiography. A large PFO may be closed by cardiologists using a transcatheter technique [171].

Breathing gases

Nitrogen narcosis

The increased partial pressure of nitrogen at depth leads to its rapid absorption into the blood and central nervous system (CNS). The action of nitrogen resembles the effect of excess alcohol or sedatives on the brain. Symptoms usually start at depths greater than 30 metres on air, but may occur on more shallow dives, and can be exacerbated by fatigue, cold, poor underwater visibility, and other drugs such as alcohol or sedatives. There is great variation between individuals in their susceptibility to nitrogen narcosis [172].

Symptoms

Commonly the affected diver is unaware that he is developing nitrogen narcosis. Symptoms include slowed mentation, increased reaction time, loss of coordination, drowsiness, euphoria, inappropriate actions, hallucinations, eventually stupor and loss of consciousness.

Treatment

Ascent to a shallower depth; abort the dive. Symptoms rapidly disappear.

Prevention

Divers must be aware of the possibility of nitrogen narcosis, particularly on dives below 30 metres. It is a common misunderstanding that divers can work up resistance to nitrogen narcosis by increasing the depth of each dive; this has been shown to reduce subjective symptoms of narcosis but does not improve the divers' performance [173].

Carbon monoxide poisoning

Carbon monoxide (CO) is a contaminant that can be inadvertently introduced into a cylinder of breathing gas while it is filled, often from poor ventilation, or the compressor inlet being close to vehicle exhaust or a person smoking. At the surface the amount of contaminant appears negligible, but at high pressure the increased concentration can cause problems which are particularly serious to a diver underwater.

Symptoms

Headache, lethargy, nausea, vomiting or loss of consciousness.

Treatment

The patient may require oxygen and hospital treatment for CO poisoning or secondary events such as partial drowning.

Prevention

Adequate ventilation and safety precautions around air compressors.

Carbon dioxide excess (hypercapnia)

A scuba diver breathes from a regulator, which has dead space and a resistance to gas flow. With increasing depth, air becomes more dense leading to additional work of breathing. Immersion in water displaces blood into the thorax from external pressure of water, reducing the lung volume and altering lung mechanics. Carbon dioxide (CO_2) is produced by metabolic activity and is increased with the effort of physical activity and the work of breathing. CO_2 build-up may quickly occur with moderate effort such as swimming against a current, particularly with poor technique or if the diver is over-weighted or physically unfit. Equipment malfunction can also cause a build-up of CO_2, as can attempts to conserve the air supply by breathing less frequently than normal

Symptoms

Increased respiratory rate, air hunger (feeling of inability to get enough air), headache, decreased awareness of surroundings, anxiety and panic.

Prevention

Adequate training and buoyancy control, physical fitness, recognition of symptoms.

Treatment

Reassure the diver, stop any active work and take slow deep breaths. The dive should be aborted before panic ensues. Most symptoms will clear rapidly, but a headache may persist for several hours.

Oxygen toxicity

At high concentrations oxygen causes CNS toxicity, leading to seizures. This is not usually of significance for a diver breathing air, but is important when gas mixtures have higher oxygen content (e.g. nitrox, where oxygen is added to reduce the nitrogen content). An underwater seizure may be lethal. Seizure onset may be sudden, or heralded by a warning prodrome including lip twitching, nausea, tinnitus, vertigo, visual disturbance, euphoria or irrational behaviour.

Pulmonary toxicity may also occur following prolonged exposure to oxygen; this is not of consequence to sports divers, but can occur during long treatments in a hyperbaric chamber. Symptoms include progressive chest tightness or discomfort, cough, dyspnoea and decreased vital capacity.

Barotrauma

'Barotrauma' describes tissue damage that occurs following a change in volume of gas in an enclosed space – such as the middle ear – after a change in pressure. Changes in gas volume with pressure are greatest in the first 10 metres of descent (Figure 18.8) and this is usually when problems arise. Inexperienced divers are more likely to experience symptoms as they are often less able to control their buoyancy. Those diving with a coincidental illness such as an upper respiratory tract infection are also susceptible. Damage occurs as soft tissue is pulled inwards to fill the space previously occupied by gas; bleeding and swelling follow. Barotrauma may occur during both descent (termed 'squeeze') and ascent from a dive.

Mask 'squeeze'

A face mask is filled with air to enable clear underwater vision. Diving masks include the nose so that pressure in this air space can be equalised by exhaling through the nose during descent. Mask squeeze is most common among inexperienced divers forgetting to equalise the pressure in the mask.

Symptoms

Facial pain, nosebleed, subconjunctival haemorrhages, petechial haemorrhages and echymosis (Figure 18.9). A nosebleed may appear severe if blood is mixed with sea water.

Treatment

Rarely needed. Bruising and swelling resolve without treatment. Unless very uncomfortable, further diving is allowed.

Prevention

Adequate training.

Suit 'squeeze'

This occurs in divers wearing dry suits. It is more common in 'membrane' type dry suits which are made of relatively thin material and tend to be a looser fit than neoprene dry suits. The suit is normally inflated with air from the cylinder to replace compressed air in the suit during descent. Failure of this system, or forgetfulness by the diver, results in the suit 'pinching' the skin causing linear marks and bruises, which may be tender and painful. No treatment is necessary. The cause of these marks is usually obvious, and the diver will recall pain in those areas during the dive. The marks should easily be distinguishable from those due to skin DCS.

Middle ear barotrauma ('squeeze')

This is the most common medical disorder to occur among divers. Middle ear barotrauma most commonly occurs during descent, and is often the result of blockage in the eustachian tube due to an upper respiratory tract infection (URTI), nasal polyps, allergies or premenstrual nasal congestion. The problem is made worse by poor technique and the diver descending too far before attempting to equalise the ears. As middle ear air is compressed, the tympanic membrane is pulled inwards causing pain (Figure 18.10). With continued descent, the mucous membrane becomes stretched, congested and oedematous, and bleeding may occur to fill the contracted space.

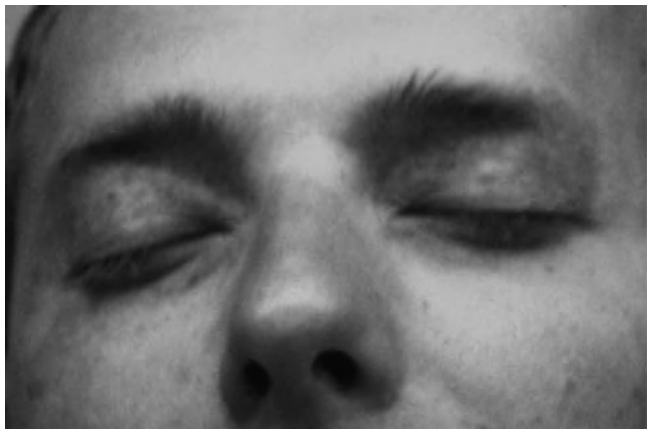

Figure 18.9 Mask squeeze, showing petechial haemorrhages of eyelids.

Symptoms

Pain, a feeling of 'fullness' in the affected ear, possible hearing loss. If the diver continues to descend, the eardrum may rupture, with relief of the pain but sudden onset of vertigo due to (cold) water entering one middle ear. Vertigo can be lethal underwater as it may be accompanied by disorientation, panic or vomiting. On surfacing, there may be conductive hearing loss, vertigo and, more rarely, tinnitus. The grades of damage found on auriscope examination are given in Table 18.19.

Prevention

There are several methods of equalisation during descent including the Valsalva manoeuvre (closing the mouth, pinching the nose shut and attempting to exhale), swallowing or wiggling the lower jaw. Divers should check whether they can clear their ears on the surface before commencing a dive and avoid diving with an URTI. Use of nasal decongestants is controversial as their effect may wear off during the dive, leading to middle ear barotrauma of ascent (see below). Ear equalisation is helped by good control of buoyancy, descent on a fixed line and descent in the upright position.

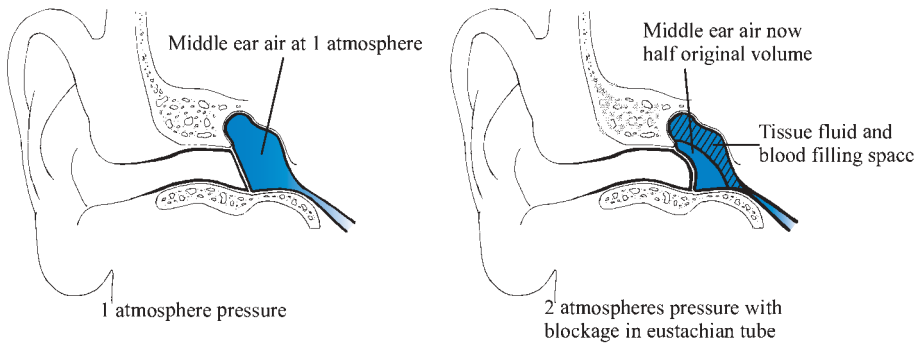

Figure 18.10 Middle ear barotrauma.

Table 18.19 Grade of middle ear barotrauma on auriscopic examination

Grade	Examination of tympanic membrane
Grade 0	Symptoms with no signs
Grade 2	Injection of the tympanic membrane
Grade 3	Injection plus mild haemorrhage within tympanic membrane
Grade 4	Free blood in middle ear
Grade 5	Perforation of tympanic membrane

Treatment

Decongestants, antibiotics if necessary and a follow-up examination before the next dive. Referral to specialist if perforation or persistent hearing loss.

Inner ear barotrauma

This is a rare but serious condition. Barotrauma leads to rupture of the round or oval windows of the inner ear, causing persistent vertigo, tinnitus, nystagmus or sensorineural hearing loss. Consultation with an otolaryngologist is required if there is evidence of haemorrhage into the middle ear, perforation of the tympanic membrane or suspected injury to the inner ear.

Sinus barotrauma

Sinus 'squeeze' is due to failure of equalisation of sinus air with the ambient pressure due to nasal congestion, allergy or nasal polyps. The lining tissue becomes congested and may bleed to fill the space.

Symptoms

Pain over the affected sinus during descent, usually relieved by ascent. Blood in the face mask due to a nosebleed, which can appear alarming underwater.

Treatment

Analgesics, decongestants. No further diving until fully recovered.

Dental barotrauma

This affects air in spaces within a diseased tooth, or between a filling and a tooth.

Symptoms

Pain in the affected tooth. Rarely, a tooth may implode during descent or explode on ascent, as swollen tissues fill the gap preventing further equalisation.

Treatment

Reassurance, analgesia and dental advice.

Pulmonary barotrauma

Pulmonary barotrauma of descent is rare, and usually occurs in breath-hold divers. It presents on surfacing as chest tightness or pain, cough, haemoptysis and dyspnoea, with pulmonary haemorrhage, alveolar infiltrates and sometimes pulmonary oedema. Treatment is supportive with oxygen; diuretics and positive pressure ventilation may be required.

Pulmonary barotrauma of ascent

This is possibly the most serious diving-related illness, and requires rapid assessment and treatment of potentially life-threatening conditions.

Pulmonary barotrauma occurs due to overexpansion of the lungs during ascent, tearing alveoli. It is usually due to breath-holding – often in a panicking diver. It is also associated with the practice of 'free ascents' when a diver breathes from scuba underwater then ascends to the surface without using the regulator to simulate an emergency ascent. This practice has mostly been banned during training. Certain pathologic lung conditions cause air trapping or slow alveolar emptying, such as mucous plugs, bronchospasm, bullous disease or cysts.

Air from ruptured alveoli may track in several ways.

1 Pneumothorax – which may rapidly become a tension pneumothorax.

2 Interstitial emphysema in the tissues of mediastinum, pericardium or neck.

3 Air enters the pulmonary venules, passing directly to the arterial circulation resulting in air embolism

1 Pneumothorax

Symptoms Recognition due to pain on the side of the burst lung, dyspnoea, tachypnoea or collapse. Must be excluded as a cause for any collapsed diver.

Treatment ABC, oxygen. Emergency relief with needle thoracocentesis. Insertion of chest drain and connection to Heimlich valve or underwater sealed drain.

2 Interstitial emphysema

Symptoms Hoarse voice, subcutaneous emphysema, swollen neck.

Treatment Reassure the diver. Exclude pneumothorax and DCS. This condition tends to resolve on oxygen and recompression is not required unless there are suspected symptoms of DCS.

The diver must not dive again without advice from a specialist diving doctor as the condition tends to recur on future dives.

3 Arterial gas embolism

See below.

Arterial gas embolism

Arterial gas embolism (AGE) is a serious and life-threatening condition. Bubbles of air enter the bloodstream through ruptured alveoli. Gas emboli pass from the pulmonary veins directly into the arterial circulation, then to the brain, spinal cord or other organs, causing serious symptoms and damage (Table 18.20). More than 90% of AGE symptoms appear within 10 minutes of surfacing. If neurological symptoms develop during this time, treatment should be provided immediately for presumed cerebral arterial gas embolism (CAGE).

Table 18.20 Symptoms of arterial gas embolism

System	Symptoms	Examination
Neurological CAGE	Loss of consciousness Convulsions Unilateral or bilateral weakness or paralysis Sensory changes, paraesthesia Visual disturbances (e.g. distorted vision or wavy lines) Confusion Aphasia Vertigo	Focal neurology Gas bubbles in retinal blood vessels Abnormal EEG
Cardiac	Chest pain	Abnormal ECG, ischaemia or dysrrhythmia
Skin	Skin marbling	

Treatment

This consists of immediate resuscitation, oxygen administration and rapid recompression (see below).

Prevention

- Medical exclusion of divers with known respiratory abnormalities.
- Avoidance of diving with concurrent respiratory tract infection.
- Adequate diver training in buoyancy control and safe ascent rates.
- Avoidance of 'free ascents'.
- Avoidance of panic; divers should only dive in conditions suitable for their level of experience [174].

Fitness to dive

Family doctors are often asked for advice on medical fitness by those planning to SCUBA dive. An understanding of the basic physics and physiology of diving medicine makes it easier to understand why certain medical conditions are not compatible with diving. Regularly updated guidelines are available online from the UK Sports Diving Medical Committee (www.uksdmc.co.uk), and advice is available from accredited medical referees. The Health & Safety Executive (HSE, www.hse.gov.uk/diving/medical) approved doctors provide rigorous medicals for professional divers. In the US, Divers Alert Network (DAN) provides online medical advice (www.diversalertnetwork.org) [175].

Diving regulations have changed to accommodate many more sports divers with chronic but well-controlled medical conditions. It is important to encourage proper training and education for those diving with a pre-existing condition. It may be necessary to tailor the type of diving and safe environment for those diving with disabilities. Recent surveys have reported up to 40% of divers with at least one chronic medical condition, including hypertension, ear and sinus problems, ischaemic heart disease and diabetes [176].

The purpose of a diving medical is to evaluate the risks and identify medical problems that:
- are made worse by diving
- make diving illness more likely
- impair performance in the water.

Medical standards

Standards are constantly being revised, so it is best to refer to current guidelines. The examples below are a brief guide

and are not inclusive. Requirements may also vary in different countries.

General physical fitness

Although recreational diving is often undemanding, an unexpected current or surge may require a high level of exertion. Diving equipment is heavy, water conditions are unpredictable and a diver may at some point have to rescue themselves or their buddy.

Obesity

Obese divers are at increased risk of DCS as nitrogen is absorbed in adipose tissue and slowly released. Obese divers also tend to be less physically fit, with less cardiovascular and respiratory reserve. Some authorities give a BMI of 30 as the maximum permitted without referral to a medical referee.

Ear, nose and throat

Perforated ear drum, blocked sinuses, inability to equalise the ears, and current ear or sinus infection are conditions that disqualify individuals from diving. Otitis externa may be caused or aggravated by contact with sea water, and may preclude the subject from diving.

Respiratory system

Lung bullae or cysts (risk of barotrauma) are contraindications to diving. Pneumothorax – a previous spontaneous pneumothorax – is a contraindication; however, if surgically treated with pleurectomy and associated with normal lung function, diving may be allowable. Refer to medical referee.

Previous traumatic pneumothorax, if healed and associated with normal lung function and thoracic CT scan, may not preclude an individual from diving. Refer to medical referee [177].

Asthma

Questions about asthma and diving are commonly asked. Most sports diving bodies allow SCUBA diving[178] if:

- asthma is childhood only
- symptoms are mild and of occasional wheeze relieved by inhaler, or asthma is stable and controlled by preventative agents
- there is normal spirometry (forced expiratory volume in 1 second FEV_1 >80% predicted and FEV_1/VC (vital capacity) ratio >70% predicted); negative exercise test (<15% fall in FEV_1 after exercise).

Subjects are not allowed to dive if:

- wheeze is precipitated by exercise, cold or emotion
- asthma symptoms require relieving medication in the 48 hours preceding a dive
- peak expiratory flow rate (PEF) has reduced more than 10% from normal.

Cardiovascular system

Hypertension: hypertensive patients are at increased risk of cardiovascular events such as stroke or myocardial infarction. Some medication such as β-blockers may limit the divers' ability to respond to exercise. Diving is allowed in mild hypertension (systolic <160 mmHg, diastolic <90 mmHg).

Divers with arrhythmias, previous myocardial infarction, pacemakers or other cardiac disease should be referred to a diving medical referee.

Diabetes

The most serious problem is a hypoglycaemic episode while underwater, which may cause abnormal behaviour or loss of consciousness. An unconscious diver cannot protect their airway and may drown. The increased physiological stress due to exercise and cold may precipitate hypoglycaemia.

Many diabetics are well controlled and take part in other types of sporting activities without problem. Diabetics are allowed to dive provided:

- the diabetic has not experienced any hypoglycaemic attacks within the past year
- diabetic control is good.
- there is no diabetic neuropathy or microvascular disease. Any retinopathy is background retinopathy only.

Epilepsy

A seizure underwater may be fatal, as the regulator mouthpiece may be lost, with aspiration of water. Medication may be sedative and may worsen nitrogen narcosis or ability to make decisions underwater. Those fit-free for 5 years and off medication are permitted to dive.

Psychiatric

Diving is allowed by subjects with depression, who are stable with or without medication. Acute psychiatric conditions are not compatible with diving.

Pregnancy

The effects on the fetus of diving during pregnancy are unknown. Currently it is not advisable to dive when pregnant [179].

Coincidental illness:

Diving is not permitted with any acute illness.

Diving accidents

It is difficult to estimate the incidence of diving fatalities as the number of divers and dives performed remains unknown. Data are collected by diving organisations such as the British Sub-Aqua Club (BSAC) in the UK, and Divers Alert Network (DAN) in the US [175]. It appears that fatalities usually result from technical rather than medical complications. Equipment problems most commonly involve buoyancy and rapid ascent. In 2006, DAN examined 75 fatalities in SCUBA divers in the US and Canada; the initial disabling events were drowning (48%), AGE (33%) and cardiac-related conditions (28%).

Divers often travel a long distance to reach a diving destination and having invested time, money and expectation will often remain determined to dive despite adverse weather conditions or coincidental illness. This has been a significant factor in many diving accidents in the UK and abroad [180]. On diving expeditions, scientists may push for a heavy diving schedule for data collection, particularly if the diving schedule has been interrupted by poor conditions, and this may result in excessive diving. Medical officers on expeditions need to ensure the safety of all expedition members and must not be persuaded into allowing diving schedules that push decompression limits.

The DAN report 2008 showed that dive computers were used for 79% of reported dives, decompression tables for 10% and 9% did not use any form of decompression schedule. Both decompression tables and dive computers are prone to user error, as well as a misunderstanding in believing that decompression sickness cannot occur within the limits of the table or computer. Due to the variety of dive computers on the market, it is not unusual for two different computers following the same dive profile to vary in decompression requirements. The discrepancy of the mathematical algorithms underpinning any dive computer or decompression table is magnified following repetitive dives. Nitrogen accumulation over several days of diving can result in DCS following a seemingly innocuous dive profile.

Expedition diving

Expedition planning and medical preparation need to start well in advance. Medical officers need to decide on an appropriate level of diving medical, depending on the medical facilities available locally as well as their own experience. Further information may be required from family doctors or through referral to a diving medical referee. While it is disappointing to be prevented from diving, serious illness in remote location could be a disaster.

Casualty evacuation (casevac) plan

A visit to the local hospital and recompression chamber facility prior to the start of the expedition can be invaluable, to establish the facilities available, introduce the medical team and make the chamber staff aware of the diving expedition, type and duration of diving. The chamber staff may also have important local knowledge about diving conditions or venomous marine life. It is also useful to determine other medical facilities (e.g. for trauma), and to find the nearest location to refill oxygen or other medical supplies.

The casevac plan should include the following.

- Recompression chamber – contact details including emergency phone numbers.
- Transport – how to arrange, contact details including emergency phone numbers.
- Type of transport (plane, boat, road vehicle) and how many patients can be taken (require a minimum of two as the buddy may also require treatment).
- If plane – is it pressurised or can it fly close to sea level?
- Distance and time likely for transport to reach dive location.
- Calculation of oxygen requirement for two people for double this length of time.
- Do medical personnel come with the transport or does the expedition medic have to go with them?
- Does the transport carry oxygen? If so, how much?
- How do you refill your oxygen for remainder of trip?

A referring medical report for an injured diver should include the following.

- Diver – name, date of birth.
- Precipitating dive – maximum depth, duration, and stops.
- Anything untoward – missed decompression or rapid ascent.
- Time of surfacing.
- Time of onset of symptoms.
- Description of symptoms and symptom progression (improving/worsening).

Table 18.21 Extra medical kit for diving expeditions

Equipment	Drugs
Oxygen cylinders × 2 (or flow splitting device) – sufficient for 2 people for duration of travel to casevac destination	Antibiotics for middle ear infections
	Decongestants
	Anti-emetics for sea-sickness
	Sun screen
Auroscope	Acetic acid 2% ear drops as prophylaxis for otitis externa
Ophthalmoscope	
Stethoscope	Gauze wicks, antibiotic/ antiseptic and corticosteroid ear drops as treatment for otitis externa
Tendon hammer	
Chest drains – assorted sizes	Vinegar to neutralise jellyfish envenomation (wear gloves to avoid contact with tentacles/nematocysts)
Sterile gloves, dressing pack	
Heimlich valve or underwater-sealed drain	
Venflons – assorted sizes	Local anaesthetic ointment
Sleek or other waterproof sticky tape	Antibiotic powder/ointment (coral cuts)
Sutures	Steroid ointment (treats persistent pruritis of coral cuts once infection treated)
Pressure bandage (and knowledge of application) for octopus/cone shell limb envenomation	Intravenous fluids (saline or Hartmanns)

- Treatment given – any relief of symptoms on oxygen?
- Previous dives during preceding days (maximum depth, duration, surface intervals).
- Past medical history, including previous DCS.
- Prescription medicines.
- Alcohol, recreational drugs.
- Allergies.

Medical kit

Some equipment and drugs may be required in addition to usual expedition supplies (Table 18.21).

In-water recompression

The decision to recompress a diver with DCS by re-immersing them in water at the dive site is not usually advocated by hyperbaric physicians. In-water recompression is a massive undertaking requiring detailed planning and equipment. It is a decision that should not be taken lightly; there is potential for further illness or death of those being treated or those assisting. However, it is something that may be considered in a remote location, particularly where long and deep dives are being undertaken, and where transfer to the closest recompression chamber would take considerable time. In-water recompression requires planning and equipment, and is discussed further in texts such as Lippmann & Mitchell [174].

References

1. Jones G (2002) What's this thing called mental toughness. *J Appl Sport Psychol* **14**: 205–218.
2. Katzenbach JR and Smith DK (1993) *The Wisdom of Teams*. Harper Collins, New York.
3. SNPFILE(2008) Sagarmatha National Park entrance statistics, Nepal.
4. Honigman B *et al.* (1993) Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Int Med* **118**: 587–592.
5. Hackett PH and Roach RC (2001) High-altitude illness. *New Engl J Med* **345**: 107.
6. Hallagan LF (1994) Who gets sick at moderate altitude? A profile of patients in Yellowstone Park. *Wild Med Let* **11**(1): 13.
7. Armstrong LE (2000) *Performing in Extreme Environments*. Human Kinetics, U.Connecticut, pp. 183–195.
8. Clark CF *et al.* (1983) Neuropsychological Functioning after prolonged high altitude exposure in mountaineering. *Aviat Space Environ Med* **54**: 202–207.
9. Dickinson J (1982) Terminology and classification of acute mountain sickness. *Br Med J* **285**: 720–721.
10. Hall W (1964) An annotated bibliography on acute mountain sickness. Natick, MA, USARIEM Report, US Army Research Institute of Environmental Medicine.
11. Silber E *et al.* (2003) Clinical features of headache at altitude: a prospective study. *Neurology* **60**(7): 1167–1171.
12. Maggiorini M *et al.* (1990) Prevalence of acute mountain sickness in the Swiss Alps. *Br Med J* **301**(6756): 853–855.
13. Maggiorini M *et al.* (1997) Association between raised body temperature and acute mountain sickness: cross sectional study. *Br Med J* **315**(7105): 403–404.
14. Loeppky JA *et al.* (2003) Body temperature, autonomic responses, and acute mountain sickness. *High Alt Med Biol* **4**(3): 367–373.
15. Hackett P and Rennie D (1979) Rales, peripheral oedema, retinal haemorrhage and acute mountain sickness. *Am J Med* **67**: 214–218.
16. Wu T *et al.* (2006) Ataxia: an early indicator in high altitude cerebral edema. *High Alt Med Biol* **7**(4): 275–280.
17. Luks AM *et al.* (2010) Wilderness medical society consensus guidelines for the prevention and treatment of acute altitude illness. *Wild Environ Med* **21**(2): 146–155.

18. Wilson MH *et al.* (2009) The cerebral effects of ascent to high altitudes. *Lancet Neurol* **8**(2): 175–191.
19. Hackett P and Roach R (2001) High altitude illness. *New Engl J Med* **345**(2): 107–114.
20. Roach R *et al.* (1993) The Lake Louise acute mountain sickness scoring system. In: Sutton J, Houston C. and Coates G (eds) *Hypoxia and Mountain Medicine: Proceeding of the International Hypoxia Symposium*, pp. 272–274. Queen City Printers, Burlington, VT.
21. Sampson J *et al.* (1983) Procedures for the measurement of acute mountain sickness. *Aviat Space Environ Med* **54**(12): 1063–1073.
22. Maggiorini M *et al.* (1998) Assessment of acute mountain sickness by different score protocols in the Swiss Alps. *Aviat Space Environ Med* **69**(12): 1186–1192.
23. Yaron M *et al.* (1998) The diagnosis of acute mountain sickness in preverbal children. *Arch Pediat Adol Med* **152**(7): 683–687.
24. Pollard AJ *et al.* (2001) Children at high altitude: an international consensus statement by an ad hoc committee of the International Society for Mountain Medicine, March 12, 2001. *High Alt Med Biol* **2**(3): 389–403.
25. Roach R (2000) Exercise exacerbates acute mountain sickness at simulated high altitude. *J Appl Physiol* **88**: 581.
26. Kayser B (1991) Acute mountain sickness in western tourists around the Thorong pass (5400 m) in Nepal. *J Wilderness Med* **2**(2): 110–117.
27. Wu TY *et al.* (2007) Who should not go high: chronic disease and work at altitude during construction of the Qinghai-Tibet railroad. *High Alt Med Biol* **8**(2): 88–107.
28. Hackett P *et al.* (1976) The incidence, importance and prophylaxis of acute mountain sickness. *Lancet* **7996**(2): 1149–1155.
29. Theis M *et al.* (1993) Acute mountain sickness in children at 2835 meters. *Am J Dis Child (1960)* **147**: 143–145.
30. Roach R (1995) How well do older persons tolerate moderate altitude? *Western J Med* **162**: 32.
31. Buddha B and James AL (1997) Medical problems of porters and trekkers in the Nepal Himalaya. *Wild Environ Med* **8**(2): 78–81.
32. Milledge J *et al.* (1991) Acute mountain sickness susceptibility, fitness and hypoxic ventilatory response. *Eur Resp J* **4**: 1000–1003.
33. Montgomery A *et al.* (1989) Incidence of acute mountain sickness at intermediate altitude. *JAMA: J Am Med Assoc* **261**: 732–734.
34. Montgomery B *et al.* (1989) Effects of dexamethasone on the incidence of acute mountain sickness at two intermediate altitudes. *JAMA: J Am Med Assoc* **261**(5): 734–736.
35. Dean A *et al.* (1990) High incidence of mild acute mountain sickness in conference attendees at 10 000 foot altitude. *J Wilderness Med* **1**: 86–92.
36. Murdoch D (1995) Altitude illness among tourists flying to 3740 meters elevation in the Nepal Himalayas. *J Travel Med* **2**: 255–256.
37. Davies AJ *et al.* (2009) Determinants of summiting success and acute mountain sickness on Mt Kilimanjaro (5895 m). *Wild Environ Med* **20**(4): 311–317.
38. Wu TY *et al.* (2009) Reduced incidence and severity of acute mountain sickness in QinghaiΓÇôTibet railroad construction workers after repeated 7-month exposures despite 5-month low altitude periods. *High Alt Med Biol* **10**(3): 221–232.
39. Hackett P (1999) The cerebral aetiology of high-altitude cerebral oedema and acute mountain sickness. *Wild Environ Med* **10**: 97–109.
40. Luks AM *et al.* (2010) High altitude. In: Mason RJ *et al.* (ed.) *Murray and Nadel's Textbook of Respiratory Medicine*, 5th edn, pp. 1651–1673. Saunders Elsevier, Philadelphia.
41. Bartsch P *et al.* (1988) Atrial natriuretic peptide in acute mountain sickness. *J Appl Physiol* **65**: 1929–1937.
42. Hacket PH and Roach RC (2007) High-altitude medicine. In: Auerbach PS (ed.) *Wilderness Medicine*, pp. 6–7. Mosby Elsevier, Philadelphia.
43. Broom J *et al.* (1994) High altitude headache: treatment with ibuprofen. *Aviat Space Environ Med* **65**: 19–20.
44. Grissom CK *et al.* (1992) Acetazolamide in the treatment of acute mountain sickness: clinical efficacy and effect on gas exchange. *Ann Intern Med* **116**: 461–465.
45. Bartsch P *et al.* (1993) Treatment of acute mountain sickness by simulated descent: a randomised controlled trial. *Br Med J* **306**(6885): 1098–1101.
46. Kasic JF *et al.* (1991) Treatment of acute mountain sickness: hyperbaric versus oxygen therapy. *Ann Emergen Med* **20**(10): 1109–1112.
47. Keller HR *et al.* (1995) Simulated descent v dexamethasone in treatment of acute mountain sickness: a randomised trial. *Br Med J* **310**(6989): 1232–1235.
48. Taber RL (1990) Protocols for the use of a portable hyperbaric chamber for the treatment of high altitude disorders. *J Wilderness Med* **1**(3): 181–192.
49. Bloch KE *et al.* (2009) Effect of ascent protocol on acute mountain sickness and success on Muztagh Ata, 7546 m. *High Alt Med Biol* **10**: 25–32.
50. Baggish AL *et al.* (2010) The impact of moderate altitude staging on pulmonary arterial hemodynamics after ascent to high altitude. *High Alt Med Biol* **11**: 139–145.
51. Muza SR *et al.* (2010) Altitude preexposure recommendations or inducing acclimatization. *High Alt Med Biol* **11**: 87–92.
52. Swenson ER and Teppema LJ (2007) Prevention of acute mountain sickness by acetazolamide: as yet an unfinished story. *J Appl Physiol* **102**: 1305–1307.
53. Luks AM and Swenson ER (2008) Medication and dosage considerations in the prophylaxis and treatment of high-altitude illness. *Chest* **133**: 744–755.
54. Moraga FA *et al.* (2007) Ginkgo biloba decreases acute mountain sickness in people ascending to high altitude at Ollague (3696 m) in northern Chile. *Wild Environ Med* **18**: 251–257.
55. Chow T *et al.* (2005) Ginkgo biloba and acetazolamide prophylaxis for acute mountain sickness: a randomized placebo-controlled trial. *Arch Intern Med* **165**: 296–301.
56. Leadbetter G. *et al.* (2009) Ginkgo biloba does – and does not – prevent acute mountain sickness. *Wild Environ Med* **20**: 66–71.
57. Headache Classification Committee of the International Headache Society (2004) The international classification of headache disorders, 2nd edn. *Cehpalalgia* **24**(Suppl. 1): 9–160.

58. Silber E *et al.* (2003) Clinical features of headache at altitude: a prospective study. *Neurology* **60**: 1167–1171.
59. Basnyat B *et al.* (2004) Neurologic conditions at altitude that fall outside the usual definition of altitude sickness. *High Alt Med Biol* **5**: 171–179.
60. Larson EB *et al.* (1982) Acute mountain sickness and acetazolamide. Clinical efficacy and effect on ventilation. *JAMA: J Am Med Assoc* **248**: 323–332.
61. Ellsworth AJ *et al.* (1987) A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. *Am J Med* **83**: 1024–1030.
62. Weil JV (2004) Sleep at high altitude. *High Alt Med Biol* **5**: 180–189.
63. Hackett PH *et al.* (1987) Respiratory stimulants and sleep periodic breathing at altitude. Almitrine versus acetazolamide. *Am Rev Resp Dis* **135**: 896–898.
64. Bloch KE *et al.* (2010) Nocturnal periodic breathing during acclimatization at very high altitude at Mount Muztagh Ata (7,546 m). *Am J Resp Crit Care Med* **182**: 562–568.
65. Luks AM (2008) Which medications are safe and effective for improving sleep at high altitude. *High Alt Med Biol* **9**: 195–198.
66. Bartsch P *et al.* (2002) Pulmonary extravascular fluid accumulation in climbers. *Lancet* **360**: 571; author reply 571–572.
67. Singh I *et al.* (1965) High-altitude pulmonary oedema. *Lancet* **191**: 229–234.
68. Bartsch P *et al.* (1991) Prevention of high-altitude pulmonary oedema by nifedipine. *New Engl J Med* **325**: 1284–1289.
69. Cremona G *et al.* (2002) Pulmonary extravascular fluid accumulation in recreational climbers: a prospective study. *Lancet* **359**: 303–309.
70. Dehnert C *et al.* (2005) Identification of individuals susceptible to high-altitude pulmonary oedema at low altitude. *Eur Resp J* **25**: 545–551.
71. Grunig E *et al.* (2000) Stress Doppler echocardiography for identification of susceptibility to high altitude pulmonary oedema. *J Am Coll Cardiol* **35**: 980–987.
72. Hackett PH *et al.* (1988) Abnormal control of ventilation in high-altitude pulmonary oedema. *J Appl Physiol* **64**: 1268–1272.
73. Luks AM (2009) Can patients with pulmonary hypertension travel to high altitude? *High Alt Med Biol* **10**: 215–219.
74. Allemann Y *et al.* (2006) Patent foramen ovale and high-altitude pulmonary oedema. *JAMA: J Am Med Assoc* **296**: 2954–2958.
75. Schoene RB *et al.* (1986) High-altitude pulmonary oedema. Characteristics of lung lavage fluid. *JAMA: J Am Med Assoc* **256**: 63–69.
76. Swenson ER *et al.* (2002) Pathogenesis of high-altitude pulmonary oedema: inflammation is not an etiologic factor. *JAMA: J Am Med Assoc* **287**: 2228–2235.
77. Sartori C *et al.* (2002) Salmeterol for the prevention of high-altitude pulmonary oedema. *New Engl J Med* **346**: 1631–1636.
78. Fagenholz PJ *et al.* (2007) Chest ultrasonography for the diagnosis and monitoring of high altitude pulmonary oedema. *Chest* **131**(4): 1013–1018.
79. Hultgren HN *et al.* (1996) High-altitude pulmonary oedema at a ski resort. *Western J Med* **164**: 222–227.
80. Hackett P (2001) High altitude and common medical conditions. In: Hornbein TF and Schoene RB (eds) *High Altitude: An Exploration of Human Adaptation*, pp. 839–885. Marcel Dekker, Inc, New York.
81. Luks AM and Swenson ER (2007) Travel to high altitude with pre-existing lung disease. *Eur Resp J* **29**: 770–792.
82. Bartsch P and Gibbs JS (2007) The effect of altitude on the heart and lungs. *Circulation* **116**(19): 2191–2202.
83. Leal C (2005) Going high with type 1 diabetes. *High Alt Med Biol* **6**: 14–21.
84. Mader TH and Tabin G (2003) Going to high altitude with pre-existing ocular conditions. *High Alt Med Biol* **4**: 419–430.
85. Luks AM *et al.* (2008) Chronic kidney disease at high altitude. *J Am Soc Nephrol* **19**: 2262–2271.
86. Dine CJ and Kreider ME (2008) Hypoxia altitude simulation test. *Chest* **133**: 1002–1005.
87. Charkoudian N (2003) Skin blood flow in adult human thermoregulation: how it works, when it does not, and why. *Mayo Clin Proc* **78**(5): 603–612.
88. Mckardle WD *et al.* (2000) *Essentials of Exercise Physiology*, Lippincott Willliams and Wilkins, Philadelphia, PA, pp. 61–62, 219–225, 429–449.
89. Bledsloe GH *et al.* (2009) *Expedition and Wilderness Medicine*, Cambridge Press, Cambridge, pp. 479–491. Ch 31.
90. Harries M *et al.* (1998) *Oxford Textbook Sports Medicine*, 2nd edn. Oxford University Press, Oxford, pp. 97–109, 272–279.
91. Rehrer NJ (2001) Fluid and electrolyte balance in ultra-endurance sport. *Sports Med (Auckland, NZ)* **31**(10): 701–715.
92. Auerbach P (2007) *Wilderness Medicine*, 5th edn. Mosby Elsevier, Philadelphia, PA, pp. 117–124, 228–283.
93. Moran DS *et al.* (1998) A physiological strain index to evaluate heat stress. *Am J Physiol* **275**: r129–r134.
94. Moran DS *et al.* (2003) Evaluation of environmental stress index for physiological variables. *J Thermal Biol* **28**(1): 43–49.
95. American College of Sports Medicine (2005) Roundtable on hydration and physical activity: consensus statements Casa DJ, Clarkson PM, Roberts WO. *Curr Sports Med Rep* **4**: 115–127.
96. Costil DL *et al.* (1976) Exercise induced sodium conservation: changes in plasma renin and aldosterone. *Med Sci Sports* **8**(4): 209–213.
97. Murray R (1987) The effects of consuming carbohydrate-electrolyte beverages on gastric emptying and fluid absorption during and following exercise. *Sports Med (Auckland, NZ)* **4**(5): 322–351.
98. Wheeler KB and Banwell JG (1986) Intestinal water and electrolyte flux of glucose-polymer electrolyte solutions. *Med Sci Sports Exercise* **18**(4): 436–439.
99. Cuddy JS *et al.* (2008) Effects of an electrolyte additive on hydration and drinking behavior during wildfire suppression. *Wilderness Environ Med* **19**(3): 72–180.
100. McGarvey J *et al.* (2010) Sensitivity and specificity of clinical signs for assessment of dehydration in endurance athletes. *Br J Sports Med* **44**: 716–719. doi: 10
101. Armstrong LE *et al.* (1994) Urinary indices of hydration status. *Int J Sport Nutr* **4**(3): 265–279.

102. World Health Organization (2006) Oral rehydration salts. Production of the new ors who/fch/cah/06.1 http://www.who.int/child_adolescent_health/documents/fch_cah_06_1/en/index.html (accessed 31 May 2012).
103. Rogers IR (2009) Hew-butler t exercise-associated hyponatremia: overzealous fluid consumption. *Wild Environ Med* **20**(2): 139–143.
104. Rothwell SP and Rosengren DJ (2011) Severe exercise-associated hyponatremia on the kokoda trail, papua new guinea. *Wild Environ Med* **19**(1): 42–44.
105. Wang SQ *et al.* (2008) In vitro assessments of uva protection by popular sunscreens available in the united states. *J Am Acad Dermatol* **59**: 934–942.
106. Pandolf KB *et al.* (1992) Human thermoregulatory responses during cold water immersion after artificially induced sunburn. *Am J Physiol* **262**: r617–r623.
107. Bouchama A *et al.* (2007) Cooling and hemodynamic management in heatstroke: practical recommendations. *Crit Care (London, England)* **11**: r54.
108. Wallae RF *et al.* (2005) The effects of continuous hot weather training on risk of exertional heat illness. *Med Sci Sports Exercise* **37**(1): 84–90.
109. Reardon MJ (1994) Army article – usariem,/mil.
110. Roberts WO (2005) Exertional heat stroke: life-saving recognition and onsite treatment in athletic settings. *The Revista Brasileira de Medicina do Esporte* **11**(6): 329e–332e.
111. Smith JE (2005) Cooling methods used in the treatment of exertional heat illness. *Br J Sports Med* **39**: 503–507.
112. Guyton AC and Hall JE (2006) *Textbook of Medical Physiology*, 11th edn. Elsevier Saunders, Philadelphia.
113. Mandsager R *et al.* (2005) State of Alaska Cold-Injury Guidelines. Review 2005. http://www.chems.alaska.gov/EMS/documents/AKColdInj2005.pdf.
114. Kornberger E *et al.* (1999) Forced air surface rewarming in patients with severe accidental hypothermia. *Resuscitation* **41**(2): 105–111.
115. Roggla M *et al.* (2002) Severe accidental hypothermia with or without hemodynamic instability: re-warming without the use of extracorporeal circulation. *Wiener klinische Wochenschrift* **114**(8–9): 315–320.
116. Holzer M *et al.* (1997) Mild hypothermia and outcome after CPR. Hypothermia for Cardiac Arrest (HACA) Study Group. *Acta Anaesth Scand Suppl* **111**: 55–58.
117. Sterz F *et al.* (1991) Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. *Crit Care Med* **19**: 379 –389.
118. Farstad M *et al.* (2001) Rewarming from accidental hypothermia by extracorporeal circulation: a retrospective study. *Eur J Cardio-Thorac Surg* **20**: 58–64.
119. Schneider SM (1992) Hypothermia: from recognition to rewarming. *Emergen Med Rep* **13**: 1–20.
120. American Heart Association (2005) American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* **112**: IV-136–IV-138. Published online before print November 28, 2005, doi: 10.1161/CIRCULATIONAHA.105.166566.
121. West J *et al.* (2007) *High Altitude Medicine and Physiology*, 4th edn. Hodder Arnold, London.
122. Golden FS *et al.* (1991) Circum-rescue collapse: collapse, sometimes fatal, associated with rescue of immersion victims. *J Roy Naval Med Serv* **77**: 139.
123. Paal P *et al.*, International Commission for Mountain Emergency Medicine (ICAR MEDCOM) (2007) Basic life support ventilation in mountain rescue. *High Alt Med Biol* **8**(2): 147–154.
124. Gilbert M *et al.* (2000) Resusciation from accidental hypothermia of 13.7°C with circulatory arrest. *Lancet* **355**(9201): 375–376.
125. Auerbach PS (1990) Some people are dead when they're cold and dead. *JAMA: J Am Med Assoc* **264**(14): 1856–1857.
126. The Hypothermia after Cardiac Arrest Study Group (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *New Engl J Med* **346**: 549–556.
127. Friberg H and Rundgren M (2009) Submersion, accidental hypothermia and cardiac arrest, mechanical chest compressions as a bridge to final treatment: a case report. *Scand J Trauma Resusc Emergen Med* **17**(1): 7.
128. Murphy JV *et al.* (2000) Frostbite: pathogenesis and treatment. *J Trauma* **48**(1): 171–178.
129. Valnicek SM *et al.* (1993) Frostbite in the prairies: a 12-year review. *Plast Reconstr Surg* **92**: 633–641.
130. West JB and Milledge JS (2000) *High Altitude Medicine and Physiology*. 3rd edn, Hodder Arnold, London.
131. Pollard AJ and Murdoch DR (2003) *The High Altitude Medicine Handbook*. Radcliffe Medical Press, Abingdon.
132. Reamy BV (1998) Frostbite: review and current concepts. *J Am Board Fam Pract* **11**(1): 34–40.
133. Lehmuskallio E (1999) Cold protecting ointments and frostbite. *Acta Derm Venereol* **79**: 67–70.
134. Imray C *et al.*, The Caudwell Xtreme Everest Research Group (2009) Cold damage to the extremities: frostbite and non-freezing cold injuries. *Postgrad Med J* **85**: 481–488.
135. Mills WJ (2002) *Clinical Aspects of Freezing Cold Injury in Medical Aspects of Harsh Environments, The Textbook of Military Medicine.* US Surgeon Generals Office, Department of the Army, USA, pp. 429–467.
136. Washburn B (1962) Frostbite. *New Engl J Med* **266**: 974–989.
137. Robson MC and Heggers JP (1981) Evaluation of frostbite blister fluid as a clue to pathogenesis. *J Hand Surg* **6**: 43–47.
138. Raine TJ *et al.* (1980) Antiprostaglandins and antithromboxanes in the treatment of frostbite. *Surg Forum* **31**: 557–558.
139. Marsigny B (1998) Mountain frostbite. *ISSM Newsletter* **8**: 8–10.
140. Oakley EHN (1996) *A Textbook of Vascular Medicine* (Tooke JE and Lowe GD, eds). Arnold, London, UK.
141. McCauley RL *et al.* (2001) Frostbite. In: Auerbach PS (ed.) *Wilderness Medicine*, 4th edn, pp. 195–211. Mosby, Philadelphia, PA.
142. Biem J *et al.* (2003) Out of the cold: management of hypothermia and frostbite. *CMAJ: Can Med Assoc J* **168**(3): 305–311.
143. Cauchy E *et al.* (2001) Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme. *Wild Environ Med* **12**: 248–255.

144. Bhatnagar A *et al*. (2002) Diagnosis, characterisation and evaluation of treatment response of frostbite using pertechnetate scintigraphy: a prospective study. *Eur J Nucl Med* **29**: 170–175.
145. Greenwald D *et al*. (1998) An algorithm for early aggressive treatment of frostbite with limb salvage directed by triple-phase scanning. *Plast Reconstr Surg* **102**: 1069–1074.
146. Barker JR *et al*. (1997) Magnetic resonance imaging of severe frostbite injuries. *Ann Plast Surg* **38**: 275–279.
147. Syme D (for ICAR Medical Commission) (2002) Position paper: on-site treatment of frostbite for mountaineers. *High Alt Med Biol* **3**(3): 297–298.
148. McCauley RL *et al*. (1983) Frostbite injuries: a rational approach based on the pathophysiology. *J Trauma* **23**: 143–147.
149. Mandsager R *et al*. (2003) State of Alaska Cold-Injury Guidelines, Rev 11/03, www.chems.alaska.gov.
150. Finderle Z and Cankar K (2002) Delayed treatment of frostbite injury with hyperbaric oxygen therapy: a case report. *Aviat Space Environ Med* **73**(4): 393–394.
151. Heimburg D *et al*. (2001) Hyperbaric oxygen treatment in deep frost bite of both hands in a boy. *Burns* **27**: 404–408.
152. Taylor MS (1999) Lumbar epidural sympathectomy for frostbite injuries of the feet. *Mil Med* **164**: 566–567.
153. Hayes DW *et al*. (2000) Pentoxifylline: adjunctive therapy in the treatment of pedal frostbite. *Clin Podiatr Med Surg* **17**(4): 715–722.
154. Bruen KJ *et al*. (2007) Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg* **142**(6): 546–551.
155. Imray CHE and Oakley EHN (2006) Cold still kills: cold-related illnesses in military practice. Freezing and non-freezing cold injury. *J Roy Army Med Corps* **152**: 218–222.
156. Imray CHE and Hillebrandt D (2004) Telemedicine and frostbite injuries. *Br Med J* **328**: 1210.
157. Ungley CC and Blackwood W (1942) Peripheral vasoneuropathy after chilling. Immersion foot and immersion hand. *Lancet* **2**: 447–451.
158. Oakley EHN (1996) Cold injury. In: Tooke JE and Lowe GDO (eds) *A Textbook of Vascular Medicine*, pp. 353–370. Arnold, London.
159. Eglin C *et al*. (2005) The effect of gentle exercise prior to a cold sensitivity test used to classify non-freezing cold injury NATO Research and Technology Organisation, Specialist meeting, Prevention of Cold injuries, Amsterdam 19–20 May 2005.
160. Khaira HS *et al*. (1998) Patellar tendon bearing orthosis- application as adjunctive treatment in healing lower limb tissue loss. *Eur J Vasc Endovasc Surg* **16**: 485–488.
161. Sumner DS *et al*. (1974) Host factors in human frostbite. *Mil Med* **141**: 454–461.
162. Iampietro PF *et al*. (1959) Responses of Negro and white males to cold. *J Appl Physiol* **14**: 798–800.
163. Duteil L *et al*. (2002) A randomized controlled study of the safety and efficacy of topical corticosteroid treatments of sunburn in healthy volunteers. *Clin Exp Dermatol* **27**: 314–318.
164. Brubakk AO and Neuman TS (eds) (2003) *Bennett and Elliott's Physiology and Medicine of Diving*, 5th edn. Saunders, London.
165. Molvaer O (2003) Otorhinolaryngological aspects of diving. In: Brubakk AO and Neuman TS (eds) *Bennett and Elliott's Physiology and Medicine of Diving*, 5th edn, pp. 227–264. Saunders, London.
166. Bove AA (1996) Medical aspects of sport diving. *Med Sci Sports Exercise* **28**: 591–595.
167. US Navy Dive Manual (2001) US Navy Dive Manual, *Revision 4*: 1–948.
168. Edmonds C *et al*. (2002) *Diving and Subaquatic Medicine*, 4th edn. Hodder Arnold, London. ISBN: 978-0-340-80629.
169. Wilmshurst P and Bryson P (2000) Relationship between the clinical features of neurological decompression illness and its causes. *Clin Sci* **99**: 65–75.
170. Mitchell SJ *et al*. (1999) Cerebral protection by lidocaine during cardiac operations. *Ann Thorac Surg* **67**: 1117–1124.
171. Wilmshurst PT *et al*. (2001) Relationship between right-to-left shunts and cutaneous decompression illness. *Clin Sci* **100**: 539–542.
172. Hamilton K *et al*. (1995) Dissociation of the behavioral and subjective components of nitrogen narcosis and diver adaptation. *Undersea Hyperbaric Med* **22**: 41–49.
173. Ross JAS *et al*. (2007) Health status of professional divers and offshore oil industry workers. *Occup Med (Oxford)* **57**: 254–261.
174. Lippmann J and Mitchell S (2005) *Deeper Into Diving*, 2nd edn. JL Publications, Melbourne.
175. Pollock NW (ed.) (2008) *Divers Alert Network Annual Diving Report*. Divers Alert Network, Durham, NC.
176. Godden D *et al*. (2003) British Thoracic Society guidelines on respiratory aspects of fitness for diving. *Thorax* **58**: 3–13.
177. Tetzlaff K and Muth CM (2005) Demographics and respiratory illness prevalence of sport SCUBA divers. *Int J Sports Med* **26**(7): 607–610.
178. Koehle M *et al*. (2003) Asthma and recreational SCUBA diving: a systematic review. *Sports Med (Auckland, NZ)* **33**(2): 109–116.
179. St Leger Dowse M *et al*. (2006) Problems associated with scuba diving are not evenly distributed across a menstrual cycle. *J Obst Gynaecol* **26**(3): 216–221.
180. Trevett AJ *et al*. (2001) Diving accidents in sports divers in Orkney waters. *Scot Med J* **46**(6): 176–177.

Online sources of information

British Hyperbaric Association: www.hyperbaric.org.uk (UK chamber information)
DAN: Divers Alert Network: www.diversalertnetwork.org
European Underwater and Baromedical Society: www.eubs.org
South Pacific Underwater Medicine Society: www.spums.org.au
Undersea and Hyperbaric Medicine Society: www.uhms.org
UK Sport Diving Medical Committee: www.uksdmc.co.uk

Chapter 19 Travel health at sea: cruise ship medicine

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Introduction

The sea has drawn adventurers, explorers and settlers, as well as the recreational traveller, to its shores and beyond for centuries. This fascination with the sea continues into the present day, with tourists flocking not only to beaches and oceanfront resorts but also to fleets of cruise ships that sail worldwide.

Travel by cruise ship has become so popular that it now constitutes the sector growing the most rapidly within the travel industry. Thirteen million people travelled by cruise ship in 2008 to a variety of destinations around the globe on the more than 161 cruise ships that make up the world's fleet, an increase from 10 million people in 2001 and a trend that is predicted to continue [1]. North American clients constitute the majority of the world's cruise line passengers with the Caribbean remaining as the top destination, followed by travel to the Mediterranean, Europe and Alaska.

The availability of qualified medical personnel in a properly equipped medical facility aboard ship is a key element in providing for the appropriate medical care and safety of a cruise line's passengers and crew members. Cruise ship medicine is the practice of medicine designed to provide cruise line passengers and crew members with timely access to comprehensive medical services for minor to severe illness and injury. It is important, however, to view a ship's medical facility as an infirmary or sickbay and not a full-service hospital. Although most of the medical conditions that arise aboard ship can be treated as they would at a doctor's office or ambulatory care centre at home, more severe problems may require emergency evacuation to a fully staffed and equipped shore-side hospital after the patient is stabilised in the ship's medical facility.

There is often a misconception, both by the general public and the medical profession, of what cruise ship medicine really entails. Many think that the maladies encountered aboard a cruise ship are limited to seasickness, sunburn and gastroenteritis, and that the doctors and nurses are merely on holiday. The reality of cruise ship medicine, however, is very different. On a weekly basis, the ship's medical staff will evaluate passengers and crew members with myriad complaints, similar to those that one would expect to see in a low-volume (though not necessarily low-acuity) emergency department, casualty clinic or ambulatory care centre (Table 19.1).

Important elements of cruise ship medicine, as well as other sectors of travel medicine, are anticipation, preparation, improvisation, observation and transportation. The ship's medical staff must try to anticipate the medical needs of the passengers and crew members and prepare for the delivery of the proper care to meet these needs. At times it may be necessary to improvise medical services owing to limitations in the shipboard medical facility's equipment, formulary and staff. A victim of serious illness or injury may need to be observed in the shipboard facility until safe transportation to an appropriate shore-side medical facility becomes available.

On average, during a 1-week cruise to the Caribbean, a ship's medical staff will see 3–5% of the passengers and 10–15% of the crew members for some type of illness or injury. Typically, more than half of all visits to the infirmary are made by crew members; 80–90% of the visits to the infirmary will be for non-urgent medical problems, 10–15% for urgent problems and 5–10% for serious illness or injury that may require temporary shipboard hospitalisation and/or emergency medical evacuation to a full-service shore-side medical facility. Fortunately, fewer than 1% of shipboard patients require emergency transfer to a shore-side hospital.

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Table 19.1 Comparison of the 10 principal diagnoses for passengers on board cruise ships versus US emergency departments [18–20]

Cruise ships		US emergency departments	
Organ system	**%**	**Organ system**	**%**
Respiratory	26–29	Injury-related and poisoning	30
Injury-related	12–18	Respiratory	12.5
Nervous and sense organs	9	Nervous and sense organs	5.7
Gastrointestinal	12–16	Gastrointestinal	5.6
Cardiovascular	3–7	Musculoskeletal and connective tissue	4.5
Genitourinary	3	Cardiovascular	4.2
Musculoskeletal and connective tissue	3	Genitourinary	4.2
Skin and subcutaneous tissue	3–13	Mental disorders	3.1
Endocrine and immune	0.8	Skin and subcutaneous tissue	2.8
Mental disorders	0.7	Endocrine and metabolic	1.4

Planning for a safe and healthy voyage

Travel can be one of life's most exciting adventures. Whether by sea, land or air, it can provide countless opportunities to explore exotic places, experience novel activities and meet a variety of interesting people. Many travellers spend a significant amount of time planning their budget, itinerary, transportation and accommodations for a trip, but they often fail to consider contingencies for unexpected illness or injury that can occur at any time or place along their journey. Foresight and preparedness for possible medical mishaps during a trip can help to avert unnecessary inconvenience or even an unforeseen disaster.

Trip readiness

The United States Coast Guard's motto, *Semper Paratus* (always prepared), is a useful concept for cruise travellers to bear in mind before the start of any voyage. This is especially important when the journey involves travel to developing countries or wilderness areas. Medical resources can be very limited or absent altogether in these areas and it may be up to the individual traveller to provide initial treatment for themself or a companion should a medical mishap occur. A major benefit of travelling by cruise ship is the availability of shipboard medical services that often exceed those available shore side at exotic ports.

Research on the destinations along the route prior to departure can be very helpful. Cruise travellers should know if there are any unusual diseases that require special precautions, immunisations or medications. Such problems include infectious diarrhoea, dengue fever, malaria, hepatitis, yellow fever and cholera. They should find out if the shore-side water is safe to drink and the food supply safe to eat without special preparation. Checking on the reliability of the area's transportation system and equipment can help to avoid motor vehicle incidents. Cruise travellers should be aware of any societal and political unrest that could interfere with their shore-side exploration. They should also use common sense when considering new adventure activities in order to avoid unnecessary injuries. The cruise lines provide much of this information to the passengers before and during their cruise. Additional information can easily be obtained from travel agents, travel literature and internet travel sites.

If planning to embark on an extensive or particularly rigorous trip, travellers should visit their healthcare provider to discuss any personal health issues that they may need to address. This is particularly important for people with chronic medical conditions, such as heart disease, lung disease, renal failure, diabetes, seizure disorders and immune disorders. They must consider the stress and physical exertion associated with long-distance land, air and sea travel, and the risks of travel outside their home territory, where medical services for their particular condition may be limited. To help minimise this stress and risk, some tour operators specialise in cruises for passengers with special medical needs, most commonly those requiring hemodialysis for chronic renal failure or oxygen for chronic lung disease. The operators provide the specialised equipment and supplies for the particular group, as well as their own medical staff of appropriate doctors, nurses and technicians to address the specific needs of the group.

It is essential that passengers with chronic medical conditions and special medical needs prepare carefully for their voyage. They should hand-carry sufficient quantities of their daily medications and medical supplies to avoid losing them in luggage misplaced during travel. Passengers can contact the cruise line passenger services or medical departments regarding any special medical needs or equipment that they may need during the cruise, such as oxygen (via portable tanks or oxygen concentrators), wheelchair, and needle and other biohazardous waste disposal containers. If not routinely available aboard ship, the cruise line can help the passenger to obtain the necessary equipment from reliable

shore-side vendors. Special staterooms for passengers with disabilities are available on most large cruise ships built over the past 10 years. These cabins can provide wider-entry doors without the usual raised threshold, wheelchair-accessible bathrooms, additional floor space, oxygen outlets, warning lights for the deaf and emergency call buttons.

For trips to exotic foreign destinations, travellers should also consider consulting a travel medicine specialist at least 6–8 weeks prior to their departure to determine if they need special immunisations or medications for the cruise. They can locate a travel medicine specialist through their own healthcare provider, local and state medical societies or other organisations, such as the American Society of Tropical Medicine and Hygiene, the International Association for Medical Assistance to Travellers and the International Society of Travel Medicine.

Travel medical insurance

A serious illness or injury while traveling can result in significant financial liability for the unfortunate tourist. Not only can out-of-pocket expenses be significant, but emergency air medical evacuation can run into tens of thousands of dollars. Medical insurance for these events can be provided by a traditional health insurer or by one specialising in health insurance for the traveller. Many people with health insurance at home will be covered for medical services in another country; however, medical providers and facilities outside of the traveller's home country may not have the capacity to invoice the traveller's insurer for services rendered and may expect direct payment from them at the time of service. It is important for travellers to review their insurance policy regarding specific coverage for services outside their local area and reimbursement for direct payment for services. United States Medicare typically does not cover medical services outside US territories. A telephone call to the traveller's health insurer prior to leaving on the trip can provide additional information on healthcare benefits while travelling. It is important to discuss precisely what medical services are covered and whether emergency air evacuation is included in the policy. If the benefits from the primary health insurance are insufficient, the traveller should consider purchasing supplemental coverage, either from the same provider or from a travel insurance company. The medical illness and injury benefit should be at least US$20,000. The emergency medical evacuation portion of the policy (for North American cruise ship passengers) should provide up to US$15,000 of coverage for trips to Alaska, Bermuda, Canada, the Caribbean and Central America; US$60,000 for travel to Europe, South America and other readily accessible locations; and up to $US100,000 for trips to Africa, Antarctica, Asia, Australia and other remote or exotic areas. The traveller should also be sure that any pre-existing medical conditions are covered by the policy.

In addition to medical and evacuation policies, various other types of travel-related insurance are available. These include trip cancellation/delay/interruption, lost luggage, tour operator default/failure, accidental death/repatriation of remains and travel assistance coverage. Home and business insurance policies, credit card programmes or transportation providers may offer limited coverage for some of these potential losses. These types of coverage are often bundled into a comprehensive insurance package along with the medical and evacuation insurance. The premium for a comprehensive insurance plan, good for the duration of the cruise or air/land tour, is typically 5–7% of the total cost of the travel package. If travellers need only supplemental medical and evacuation insurance, it can cost as little as US$50 per person for a year's coverage.

Traveller's first-aid kit

Most illnesses and injuries incurred while travelling are not life threatening; however, if travellers are not prepared to treat them they can easily disrupt an otherwise enjoyable trip. A personal first-aid kit is an efficient way to prepare for these unexpected emergencies, both while travelling and at home. A standard kit can be purchased at most pharmacies and sporting goods stores or travellers may wish to design a specialised first-aid kit that meets their own particular needs (Table 19.2).

A small tote bag is a convenient way to store all of the supplies in the kit. It allows enough room for the essential items and it ensures easy portability for travel. Certain items should be included in any first-aid kit. A small flashlight is very handy if there is a power cut or if the kit is needed out of doors. A pen and notepad help to keep track of supplies and make notations about important incidents. A pair of rounded-tip scissors is useful for cutting bandages and other items. Tweezers, safety pins and a Swiss Army-type knife are all tools that have multiple uses. Tape, bandages, cotton swabs, antibiotic ointment and blister dressings are used to treat cuts, scrapes and blisters. Elastic wraps and triangular bandages can help immobilise injured limbs. Rubber gloves provide a protective barrier to reduce the risk of infection when treating open wounds. Acetaminophen, aspirin and ibuprofen are effective for the treatment of pain or fever. Non-prescription medications for colds, allergies, motion sickness, heartburn and diarrhoea are commonly needed when travelling. Sunscreen and insect repellent are important for trips to sunny and insect-prone destinations. It is important for the cruise traveller to include an adequate supply of any prescription medications, including spectacles and/or contact lenses, to last the entire trip. They should also

Table 19.2 Suggestions for a traveller's first-aid kit

A small flashlight is very handy if there is a power outage or if the kit is needed out of doors
Pen and notepad to keep track of supplies and make notations about important incidents
Aspirin, acetaminophen or ibuprofen are effective for the treatment of pain and fever
Acetaminophen is the preferred medication for children with fever
Oil of cloves for toothache
A pair of round-tipped scissors is useful for cutting bandages and other items
Tweezers, safety pins and a Swiss Army-type knife are all tools that have multiple uses
Tape, bandages, cotton swabs and antibiotic ointment are used to treat scrapes, cuts and burns
Blister dressings
Elastic wraps and triangular bandages can help immobilise injured limbs
Instant ice pack (or disposable freezer bag)
Rubber gloves protect your hands and reduce the risk of infection when treating open wounds
Thermometer with case
Spectacle repair kit
Spare spectacles, contact lenses and sunglasses
Antihistamine/decongestant medications for allergic symptoms and congestion.
Eye drops
Cough medicine and throat lozenges
Lip balm, canker gel, dental floss
Hydrocortisone cream for insect bites and itch
Antifungal cream for athlete's foot and yeast infections
Antacid and heartburn relief tablets
Laxative and antidiarrhoeal medication
Sunscreen, factor 15 or greater
Sea/motion sickness tablets
Insect repellent when traveling to insect-prone destinations
Personal medications and prescriptions
Personal medical information form

All medications should be stored out of reach of children; only products with child safety caps should be used.
First-aid kits should be in a carry-on bag, not in checked luggage.

enclose a written list or copies of their medication and spectacle prescriptions in the kit.

The final component of the first-aid kit should be a personal medical information form (Figure 19.1). This is a convenient way of ensuring that essential medical information will be available to travelling companions and medical personnel when needed. The form identifies the next of kin, doctors, hospital and insurance carrier. It lists any past and present illnesses, medications, allergies, blood type and immunisation status. People with a history of heart disease may want to attach a copy of their most recent electrocardiogram (ECG). The form indicates who is to be notified in an emergency. That person should have a copy of the form outlining the traveller's entire medical history.

Medical care at sea

Many people think of a cruise as the trip of a lifetime. For others it is the only way to travel. A modern cruise ship offers one of the most luxurious and safe ways of exploring international destinations. From the smaller ships of less than 100 m in length, which carry fewer than 100 passengers, to the truly titanic 300 m vessels sailing with more than 3,000 passengers and 1,000 crew members, cruise ships provide their guests with amenities that rival, and even exceed, those experienced at renowned shore-side resorts. A beautiful vessel, luxurious accommodation, great food, the leisurely life at sea and exotic ports of call all add up to a fabulous holiday. But what if the unexpected happens and the cruise traveller suddenly becomes ill or injured? They are far away from home on the high seas and in need of prompt evaluation and treatment. It is comforting to both passengers and crew members to know that the ship's medical staff is just a few decks away.

Cruise ship medical facility

Several factors influence the specific requirements for medical staff and equipment onboard a cruise ship. These include the following.

- The size of the ship.
- The total number of passengers and crew members.
- The average age of the passengers, their baseline health status and their planned activities. Industry-wide, the average cruise line passenger is 45–50 years of age. Certain cruise lines attract a senior clientele, while others cater to the younger crowd. An older age group will tend to have more chronic medical problems, such as heart and lung disease, which may flare up while they are travelling. A younger age group may have more injuries due to alcohol use and sports activities.
- The destination and length of the cruise. Longer periods away from the home port, especially days at sea, necessitate stocking up on more frequently used supplies. Common ailments, such as respiratory infections, may increase in frequency on longer cruises. Knowledge of the types and quality of medical facilities along the itinerary is important to determine whether passengers or crew members can be sent shore side for additional care or whether they need to be evacuated by air back to the home port.

Personal Medical Information Form

Name:	Date of Birth:
Street:	
City:	Social Security Number:
State/Province:	Passport Number:
Postal/Zip Code:	
Country:	Telephone Number:

Health Insurance Plan **Supplemental / Travel Insurance Plan**

Provider:	Provider:
Member ID Number:	Member ID Number:
Street:	Street:
City:	City:
State/Province:	State/Province:
Postal/Zip Code:	Postal/Zip Code:
Telephone Number:	Telephone Number:

Doctor **Hospital**

Name:	Name:
Street:	Street:
City:	City:
State/Province:	State/Province:
Postal/Zip Code:	Postal/Zip Code:
Telephone Number:	Telephone Number:

Emergency Contact Person

Name:	Relationship:
Street:	
City:	Telephone Number:
State/Province:	
Postal/Zip Code:	

Present & Past Medical Conditions

Figure 19.1 An example of a personal medical information form.

Allergies & Drug Sensitivities

Blood Type

Medications

Name (generic)	Dose	Schedule

Vaccines & Preventative Medications

Type	Yes	No	Date Last Received
Routine Immunizations:			
DTP, Td (diphtheria-**tetanus**-pertussis)			
Haemophilus influenza B (sepsis)			
Influenza			
MMR (measles-mumps-rubella)			
Pneumococcus (pneumonia)			
Polio			
Varicella (chicken pox)			
*Other: (as determined by destination)**			

*Cholera, hepatitis A, hepatitis B, immune globulin, Japanese encephalitis, malaria prophylaxis, meningococcal meningitis, plague, rabies, tick-borne encephalitis, tuberculosis, typhoid fever, yellow fever

If you have a history of heart disease please attach a copy of a recent **EKG**.

Provide a copy of this form to family members and emergency contact designees.

Take this form with you when you seek medical attention.

Figure 19.1 (*Continued*)

A well-designed cruise ship medical department requires careful planning. Adequate space must be assigned in the architectural plans of the ship to allow for the delivery of necessary medical services for passengers and crew members. The medical facility must be equipped with essential diagnostic and therapeutic supplies and equipment. An efficient medical care delivery system is needed in order to meet the needs of passengers and crew members, despite limitations in equipment and staff when compared with a shore-side hospital. There should be a contingency plan in place to provide emergency medical services in designated locations in the event of an onboard disaster and the primary medical facility becoming inaccessible due to fire, smoke or water damage. Most importantly, the medical department must be staffed by qualified doctors and nurses who are capable of working in an isolated environment. The final plan for any particular medical department will also be influenced by the ship's size and design, total number of passengers and crew members, guest demographics, expected number of medical facility patient visits and the ship's itineraries.

Previously, most cruise lines worked independently to address these shipboard medical facility issues. In 1990, however, the American College of Emergency Physicians (ACEP) Cruise Ship and Maritime Medicine Section was founded and created a forum for cruise ship medicine practitioners and others in the cruise industry to discuss these topics.

The Cruise Ship and Maritime Medicine Section was organised by members of the ACEP experienced in the practice of cruise ship medicine. The objectives of the Section are to:

1 serve as a resource to the cruise industry, their medical departments, and physicians interested in cruise ship medicine

2 develop guidelines for quality and consistent medical care aboard cruise ships

3 encourage research on cruise ship medicine

4 provide educational opportunities for cruise ship medical and administrative staff members

5 promote the importance and enhancement of onboard medical care

6 educate the medical establishment about the content and complexity of cruise ship medicine.

There are minimal international maritime regulations pertaining to medical services aboard cruise ships and these mainly address the needs of the crew members, not cruise ship passengers; for example, there is no international requirement to have a doctor aboard ship. Additional regulations may apply to cruise ships depending on the country of registry, but many of these regulations are vague in nature and do not address specific recommendations for a cruise ship's medical facility or its medical staff.

One of the major accomplishments of the ACEP Cruise Ship and Maritime Medicine Section has been the development of the *Health Care Guidelines for Cruise Ship Medical Facilities*, first released in 1995 and revised in 1997 and 2010 [2] (*see* Additional resources). The guidelines are the recommendations of several cruise line medical directors and experienced ship's physicians from within the industry and authorised to practise medicine in US, British, Canadian, Norwegian and other land-based facilities. The guidelines provide invaluable assistance to cruise ship medicine practitioners in the development of shipboard medical departments, and to the cruise industry as a quality improvement tool for medical services at sea.

These guidelines are an adjunct to the international maritime safety regulations (International Safety Management Code [ISM], Safety Management System [SMS] and Safety of Life at Sea [SOLAS]) as established by the International Maritime Organization and International Labor Organization. The International Council of Cruise Lines (ICCL), a major cruise industry trade group based in the US and representing 16 of the world's largest cruise lines, has adopted a modified version of the guidelines for its membership. The major cruise lines sailing to US ports and many other cruise lines worldwide currently adhere to the ACEP and ICCL guidelines on a voluntary basis. The ICCL works within the cruise industry to integrate the guidelines into the ISM code and the SMS as the standard for medical services aboard cruise ships.

The ACEP Cruise Ship and Maritime Medicine Section undertakes regular reviews of the *Health Care Guidelines for Cruise Ship Medical Facilities* for another revision. Topics on which guidance are provided include to the Policy Resource and Education Paper (PREP), which includes recommendations for a standardised formulary list, contingency plans for medical services in the event that the infirmary becomes inaccessible, expanded laboratory capabilities, travel insurance, emergency evacuation procedures and shore-side medical facility evaluation.

The World Health Organization implemented the International Health Regulations in 2005 and enforced them in 2007. They provide regulations to enhance national, regional and global public health worldwide. The regulations are internationally binding and include reference to water and sanitation on ships and ports among others [3].

Cruise ship physician

The cruise ship physician's main responsibility is to provide medical services for all shipboard personnel and passengers. They are also involved in public health, hygiene and safety issues on board ship. In addition, the physician is a ship's senior officer who represents not only the medical

department but also the ship and the cruise line. The ship's physician should never underestimate their responsibilities aboard ship, nor overestimate their authority. Cruise ships typically have a strict hierarchy of command and it is very important that the physician keep superiors informed of any health issues that could impact the ship's operations, such as an infectious disease outbreak or the need for an emergency medical evacuation.

As with the cruise industry in general, cruise ship medicine is made up of an international group of participants. North American physicians staff about 10% of the world's fleet. Physicians from various countries, such as the UK, Norway, Sweden, Denmark, Greece, Italy and South Africa, staff majority of the remainder. Tours of duty aboard ship run from a few weeks to several months, as determined by the respective cruise line's staffing policy. Depending on the size of the ship and the number of passengers and crew members, the doctor may be the only medical staff member aboard ship or they may be part of a medical team consisting of an additional doctor and three to five nurses. Cruise ship nurses are typically well trained and experienced in emergency and critical care services. They play a pivotal role in providing quality medical care to the passengers and fellow crew members. They also often serve as triage officers for the ship's sickbay and office managers for the medical department.

Shipboard maladies

Although the types of illness and injury encountered aboard a cruise ship are similar to those seen at shore-side outpatient clinics, there are certain medical problems that many people associate with ocean travel or that pose particular diagnostic and therapeutic dilemmas when they arise on board a ship. It is important for the ship's medical staff to be familiar with the common illnesses and injuries that that are seen aboard ship and be prepared to treat and stabilise patients with life-threatening conditions, who can also present to the ship's infirmary.

Sea sickness

Sea sickness is a primary concern for many cruise travellers, but in reality it is seldom a significant problem. Most cruise itineraries are in calm seas and modern cruise ships have port and starboard stabilisers that help to minimise excessive motion in rougher waters. Unfortunately, some people are very sensitive to the motion not only of ships but also aeroplanes, automobiles, trains and amusement park rides. These cruise ship passengers are more likely to develop sea sickness even in smooth seas. As the churn of the sea increases, so does the incidence of sea sickness among both passengers and crew members. Nearly everyone will eventually exceed their threshold for sea sickness as ocean conditions worsen.

Humans sense their orientation in three-dimensional space via visual input from the eyes, proprioceptive input from muscles and joints, and vestibular (apparatus) input from the inner ear. Sea sickness, as well as motion sickness in general, is currently considered to be caused by visual, proprioceptive and vestibular sensory conflict, or neural mismatch, that results in the cholinergic stimulation of the brain's vomiting centre and the parasympathetic nervous system. Hence, signs and symptoms of sea sickness can range from a vague feeling of being 'unwell' to headache, pallor, anxiety, warmth, cold sweats, fatigue, dizziness, vertigo, and finally nausea and vomiting [4].

Several factors can influence one's susceptibility to sea sickness. An unfamiliar pattern of motion, such as that encountered aboard a boat or ship, is the main cause of symptoms. A ship's motion can be categorised as roll (rotation around the ship's longitudinal axis), pitch (rotation around the horizontal axis), yaw (rotation around the vertical axis) and heave (movement along the vertical axis). Although rhythmic motion around any one of these axes can precipitate sea sickness, it is typically a combination of these movements that one encounters at sea. A roll, pitch, yaw or heave periodicity of one cycle every 2–5 s (0.2–0.5 Hz) is most effective in causing symptoms when compared with other periodicity rates. Adaptation to the motion tends to occur over 2–3 days as cruise travellers get their 'sea legs' and symptoms then often abate. Infants under the age of 2 years are rarely affected, whereas children between the ages of 4 and 12 years are most likely to become ill from the adverse motion. Women tend to be more prone to sea sickness than men, especially when pregnant. Overzealous dietary intake or excessive alcohol consumption can aggravate the symptoms of sea sickness. In rough seas when many people become afflicted, a psychosomatic component may trigger sea sickness in travellers who otherwise could weather the storm.

The treatment of sea sickness can be approached using environmental alterations, pharmacological agents and non-pharmacological devices. Since the unfamiliar rhythmic motion encountered aboard ship is the major precipitant of sea sickness, actions to minimise the motion can be effective in preventing progression of symptoms. These include moving amidships near the vessel's centre of gravity, where the motion should be less pronounced. Stepping out on deck for some cool fresh air and looking off to the horizon may help to diminish the conflicting visual sensory input. Stateroom location aboard ship has been considered to be a factor for the incidence of sea sickness, those closer to the centre of the ship having less motion and their occupants suffering

less sea sickness, but a recent small study disputes this [5]. What may be more important is the actual position of the occupant. A supine position parallel to the axis of major motion helps to minimise the effects of the motion on the vestibular apparatus in the inner ear. Closing the eyes to inhibit visual stimulation and stabilising the head with pillows to prevent side-to-side motion help to decrease contradictory visual and vestibular sensory input.

Mal de débarquement is another disorder that is associated with ocean travel. Following a few days at sea, with or without suffering from sea sickness, the cruise ship passenger may develop symptoms of motion sickness *after* returning to terra firma in port. This is felt to be a result of the traveller's habituation to the motion of the ship and the sudden exposure to the now unfamiliar absence of motion. Symptoms are usually mild and resolve within hours or a few days. More severe or protracted symptoms warrant consideration of other conditions such as benign paroxysmal positional vertigo and Ménière's disease. Mal de débarquement syndrome (MDDS) is a chronic form of this disorder. What causes MDDS is unclear. Vestibular dysfunction, depression, hormonal imbalance and migraine variant have all been proposed as possible aetiologies. Symptoms can be mild to severe and persist for many years. Treatment regimens may include the use of sedatives, antidepressants, female hormones and physical therapy [6].

The pharmacological treatment of sea sickness involves the use of various antihistamine, anticholinergic and antiemetic agents (Table 19.3). The antihistamine medications dimenhydrinate, meclozine, cyclizine, buclizine, cinnarizine and diphenhydramine are the most widely used drugs for sea sickness. They can be very effective in preventing sea sickness if ingested 1–2 h prior to embarking on a voyage. When taken in the recommended doses, these drugs have minimal side effects, mainly mild sedation and dry mouth.

Hyoscine (scopolamine) in the form of a transdermal patch is one of the most effective prophylactic medications for sea sickness. The 1.5 mg unit dose patch is placed behind the ear at least 4 h prior to sailing. The patch can be left in place for 3 days and then replaced if needed. Up to 60% of users develop a dry mouth, but drowsiness is less common than with the antihistamine and antiemetic medications. Other potential side effects include blurred vision, urinary retention (especially in older men), confusion and hallucinations. Due to the unit dosing, people with a smaller body mass may be more prone to side effects. Hyoscine in tablet form, often taken with dexamfetamine or ephedrine to counteract drowsiness, is also very effective for the prevention and treatment of sea sickness.

Antiemetic medications are typically given parenterally or via rectal suppository to people who are vomiting or are having progressive symptoms despite taking the primary oral medications. Promethazine, prochlor-perazine, metoclopramide and trimethobenzamide are all very effective in alleviating the nausea and vomiting of sea sickness. As with the antihistamines, their anticholinergic effects also decrease the efferent cholinergic impulses from the vestibular apparatus.

Ginger root is a popular alternative herbal treatment for sea sickness. It can be used either as a preventative or for the active treatment of symptoms. One gram is typically taken in tablet or capsule form prior to the start of the voyage. It may then be repeated every 6–12 h as needed. The most common side effect associated with prolonged ginger root use is dyspepsia [7].

Non-pharmacological therapy for sea sickness is also available. Wrist bands that apply acupressure or electrical stimulation to the palmar surface of the wrists may be helpful in preventing sea sickness. The basis for their use is the stimulation of the P6 or Neiguan acupuncture point at the wrist. The acupressure wrist bands have been shown to

Table 19.3 Medications commonly used for the prevention and treatment of sea sickness

Medication	Dose
Antihistamines	
Buclizine	50 mg p.o. 6–8 h
Cinnarizine	15–30 mg p.o. 6–8 h
Cyclizine	50 mg p.o. or i.m. 4–6 h
Dimenhydrinate	25–50 mg p.o. or i.m. 4–6 h
Diphenhydramine	25–50 mg p.o. or i.m. 4–6 h
Meclozine	25 mg p.o. 6–8 h
Anticholinergics	
Hyoscine (scopppolamine)	1.5 mg transdermal patch, 72 h 0.3 mg p.o. 4–6 h (also taken in combination with dexamfetamine 5 mg or ephedrine 25 mg)
Antiemetics	
Metoclopramide	10 mg p.o., i.m. or i.v. 6–8 h
Prochlorperazine	10 mg p.o., i.m. or i.v. 6–8 h 25 mg p.r. 12 h
Promethazine	25 mg p.r. or i.m. 4–6 h 25 mg p.o. 4–6 h (also taken in combination with ephedrine 25 mg)
Trimethobenzamide	250 mg p.o. 6–8 h 200 mg p.r. or i.m. 6–8 h
Other	
Ginger root	1 g p.o. 6–12 h

decrease the morning sickness associated with pregnancy, but studies evaluating the use of these and the electrical stimulation wrist bands for sea sickness have provided conflicting results [8, 9].

Respiratory illness

Respiratory ailments constitute the most common diagnosis in most ships' infirmaries. This is merely a manifestation of what one might term the traveller's respiratory syndrome. As they travel long distances over several hours or days in crowded trains, planes and cruise ships, travellers are often exposed to dry, recirculated air, a variety of unfamiliar viral and bacterial pathogens, and new environmental allergens. All of these factors can contribute to inflammation and infection of the upper respiratory system in healthy individuals and aggravate respiratory conditions in others with chronic problems. Most of these cases are self-limited and the patients can be treated symptomatically with fluids, antipyretic, antitussive and antihistamine medications. Should a bacterial infection be suspected or diagnosed, appropriate antibiotics can be administered from the ship's pharmacy.

Outbreaks of influenza A have occurred aboard cruise ships worldwide and have been widely reported, including outbreaks in New England, Alaska, the Mediterranean and Australia [10–12]. In some cases the outbreak occurred outside the area's typical influenza season, with the virus being imported from another hemisphere with an active influenza season. Passengers unknowingly carried the virus to the various ships, infecting other guests and crew members. Although the cruise ships were not the actual source of the virus, they unfortunately became a reservoir for the virus on later cruises. The outbreaks were brought under control with antiviral medications and influenza vaccination for susceptible passengers and crew members. Annual influenza vaccination programmes were then instituted for all crew members to prevent recurrent outbreaks during subsequent cruise seasons. In addition, active and passive influenza surveillance programmes were instituted by several major cruise lines to assist in the early detection of any new outbreaks. In light of these outbreaks and others worldwide, and the ease of modern international travel from continent to continent and hemisphere to hemisphere, influenza is no longer considered to be a truly seasonal disease [13].

Food- and water-borne illness

Isolated cases of gastrointestinal illness aboard cruise ships are common, comprising 5–10% of sickbay visits. Many of these cases are precipitated by changes in diet, overindulgence, and food and water ingested off the ship in developing countries. Fortunately, outbreaks of food- and water-borne illness are rare. As with shore-side outbreaks, more than half are due to the Norwalk (or related) virus or an undetermined agent. The rest are due to a variety of bacterial agents, most notably enterotoxigenic *Escherichia coli*, salmonella, shigella, *Staphylococcus aureus*, *Clostridium perfringens* and campylobacter [14].

The cruise industry is ever vigilant to ensure that the water and food stores aboard its ships are safe and reliable. An outbreak of food- or water-borne illness on a cruise ship can potentially afflict hundreds of passengers and crew members in a very short time. It can also quickly tarnish the reputation of even the most respected cruise line, as well as the cruise industry as a whole. A study by the United States Centers for Disease Control and Prevention (CDC) on the epidemiology of diarrhoeal disease outbreaks on cruise ships between 1986 and 1993 revealed that the incidence was only 2.3 outbreaks per 10 million passenger days (equivalent to a 1,500-passenger ship sailing 50 weeks per year having a single outbreak once every 10 years). They noted that the incidence of outbreaks had decreased by nearly a third since the previous study period, 1980–1985. The CDC also suggested that a significant further decrease in future outbreaks could be accomplished merely by:

- thoroughly cooking all meat, fish and poultry
- using pasteurized eggs for all pooled egg recipes
- not allowing food handlers to work with any gastrointestinal symptoms
- not using onshore food vendors where quality control may be diminished [15].

The Vessel Sanitation Program (VSP), developed and administered by the CDC, has been instrumental in the steady decline of gastrointestinal outbreaks aboard cruise ships. The VSP was established in 1975 as a cooperative activity with the cruise industry to develop and implement comprehensive sanitation programmes aimed at minimising the risk of gastrointestinal diseases. Biannual, unannounced food safety and environmental sanitation inspections are performed on all vessels with a foreign itinerary calling at a US port and carrying 13 or more passengers. The Vessel Sanitation Inspection Report, with a possible maximum score of 100, is completed during the inspection. A score of 86 or higher is considered to be satisfactory. Lower scores result in an unsatisfactory rating for the vessel and require immediate corrective action. Inspection results are compiled in the VSP 'Green Sheet', which is made available to the public via mail and the CDC website [16].

In addition to the VSP, cruise lines utilise the Hazard Analysis Critical Control Point (HACCP) programme to help prevent food-borne illness aboard ship. The HACCP programme outlines procedures to ensure the proper storage, handling and preparation of food. It also addresses hygiene

and sanitation regulations for food handlers and food preparation areas [17].

Critical care at sea

A critically ill patient can be difficult to manage even in a full-service shore-side hospital. The critically ill passenger or crew member on board a cruise ship can provide a significant challenge for even the most seasoned cruise ship physician. With limited diagnostic equipment and medical staff available aboard ship, the physician's main resource for properly diagnosing and treating the patient may be their own clinical skills and experience. Admitting a patient from your hometown emergency department into the intensive care unit is relatively easy, but arranging for a costly emergency medical evacuation that requires diversion of the ship to another port, or air transport to an appropriate medical facility, must be coordinated with the ship's master (captain) and other superiors. The physician must take these logistical issues into consideration when deciding whether to keep a critically ill patient aboard ship or disembarking them to an 'appropriate' shore-side medical facility that may be hundreds or even thousands of miles away via air transport.

A helicopter rescue at sea may be an exciting spectator sport for the ship's passengers, but it is used only as a last resort for patients who must get to a shore-side medical facility immediately, such as for severe gastrointestinal bleeding, cardiogenic shock, surgical abdomen, massive trauma or any other condition where time to definitive treatment is critical. A helicopter rescue is inherently dangerous because the helicopter must hover above the ship and the patient is raised in a basket. A crash of the helicopter on to the ship would undoubtedly result in extensive damage to the helicopter and ship, and possibly multiple casualties on board both vessels. Therefore, most patients are stabilised aboard ship and then disembarked at the next available port.

The spectrum of serious illness and injury seen aboard cruise ships is very broad. Although incidents do occur that result in multiple trauma, most critical patients suffer from a variety of medical problems that include acute respiratory failure, stroke, gastrointestinal bleeding, acute abdomen, sepsis, ectopic pregnancy and abdominal aortic aneurysm. A particular concern is the patient with massive haemorrhage. Blood is not stored on board cruise ships. It is seldom needed, requires a special refrigeration unit and it has a short storage life of 35–40 days. However, when the need arises, it is most urgent that blood be made available. All efforts are made to obtain typed and screened O-negative blood from reliable shore-side sources in a timely fashion. If necessary it can be dropped from an aircraft to the ship. If banked blood is not available and the patient is at high risk of dying from the blood loss, then blood can be obtained from previously screened and low-risk crew members. Using simple diagnostic kits, the blood is typed, tested for HIV and then transfused to the patient. Such unconventional improvisation has proven to be life saving during these critical episodes.

The most common critical illness encountered is acute myocardial infarction. As in most industrialised countries, this is also the leading cause of death on cruise ships. Patients may initially present with sudden cardiac arrest, but more often they arrive at the infirmary to be evaluated for chest pain. As is done at shore-side medical facilities, they are promptly placed on a cardiac monitor and nasal oxygen and intravenous access is obtained. Evaluation of their chest pain includes a medical history, physical examination and ECG. If the ECG is consistent with acute myocardial infarction and there are no contraindications to its use, a fibrinolytic agent is given to abort the infarction, along with aspirin, heparin and a beta blocker, as per established advanced life support (ALS) guidelines. An initial non-diagnostic ECG will prompt blood tests for serial cardiac enzymes (using bedside diagnostic kits for myoglobin, CK-MB and troponin I) and serial ECGs. If a diagnosis of acute myocardial infarction can be made, fibrinolytic therapy is then reconsidered. If all tests are negative over a 6–8 h observation period and the patient is symptom-free, they can be released from the infirmary and advised to limit physical activity until re-evaluated the following day.

Cruise ship telemedicine

Although often viewed as a recent development, telemedicine has been used for decades to extend the reach of medical experts. The current state-of-the-art real-time videoconferencing is at one end of the telemedicine spectrum – very complex, very expensive. Near the other end are the less complex, less expensive applications. With respect to the maritime industry, these include the signal flag, the two-way radio, the satellite telephone/fax and more recently the internet.

Telemedicine allows the often isolated cruise ship physician and nurse to consult with a specialist concerning a perplexing diagnosis or difficult case management. It also allows the ship's medical staff to provide consultation services to others in need. A few of the newer cruise ships have the capability for real-time videoconferencing, but its utilisation has been limited. Qualified cruise ship physicians can manage most cases that they are presented with, and most consultations can be done over a radio or satellite telephone. If graphical information (ECG, photographs) is requested by the consultant, it can be sent via fax or email. A particularly useful shipboard telemedicine component is the digitised radiograph. The radiograph can be sent over the internet via

satellite to a radiologist anywhere in the world for either a primary diagnostic reading or as part of a quality management programme. Regardless of what telemedicine modality is available on board a particular ship, it should be considered merely as a communications tool that can be used to enhance the medical services aboard ship. It must never be viewed as a substitute for a qualified and experienced cruise ship medical staff.

References

1. Cruise Lines International Association (2009) CLIA Cruise Market Overview: Statistical Cruise Industry Data Through 2008. Cruise Lines International Association, Fort Lauderdale, FL. http://www.cruising.org/sites/default/files/pressroom/2009_Market_Overview.pdf (accessed 27 June 2012).
2. American College of Emergency Physicians (2012) Health Care Guidelines for Cruise Ship Medical Facilities. American College of Emergency Physicians, Dallas. http://www.acep.org/practres.aspx?LinkIdentifier=id&id=29980&fid=2184&Mo=No (accessed 17 June 2012).
3. World Health Organization (2005) International Health Regulations. World Health Organization, Geneva. http://www.who.int/ihr/en/ (accessed on 27 June 2012).
4. Gahlinger P (2000) Cabin location and the likelihood of motion sickness in cruise ship passengers. *J Travel Med* **7**: 120–124.
5. Gahlinger P (1999) Motion sickness, how to help your patients treat travel travail. *Postgrad Med* **106**: 177–184.
6. Hain TC *et al.* (1999) Mal de debar-quement. *Arch Otolaryngol* **125**: 615–620.
7. Udani J (1998) Ginger for motion sickness, hyperemesis gravidarum and anesthesia. *Altern Med Alert* **1**(12): 133–144.
8. Bruce D *et al.* (1990) Acupressure and motion sickness. *Aviat Space Environ Med* **61**: 361–365.
9. Hu S (1995) P6 acupressure reduces symptoms of vection-induced motion sickness. *Aviat Space Environ Med* **66**: 631–634.
10. CDC (1998) Outbreak of influenza A infection: Alaska and the Yukon Territory, June–July 1998. *MMWR Morb Mortal Wkly Rep* **47**: 638.
11. CDC (1998) Outbreak of influenza A infection: Alaska and the Yukon Territory, June–August 1998. *MMWR Morb Mortal Wkly Rep* **47**: 685–688.
12. Health Canada (1998) Influenza a outbreak on a cruise ship. *Canada Communicable Dis Rep* **24**: 9–11.
13. CDC (1999) *Preliminary Guidelines for the Prevention and Control of Influenza-Like Illness Among Passemgers and Crew Members on Cruise Ships*. Centers for Disease Control, Atlanta, GA.
14. CDC (2001) Diagnosis and management of foodborne illnesses: a primer for physicians. *MMWR Morb Mortal Wkly Rep* **50** (RR-2).
15. Koo D (1993) Epidemiology of diarrheal disease outbreaks on cruise ships, 1986 through 1993. *JAMA: J Am Med Assoc* **275**: 545–547.
16. CDC (2000) *Vessel Sanitation Program Operations Manual*. Centers for Disease Control, Atlanta, GA.
17. US Department of Health and Human Services, Public Health Services, FDA (1999) *Food Code*. USDHHS, Washington, DC.
18. Dahl E (1999) Anatomy of a world cruise. *J Travel Med* **6**: 168–171.
19. Peake D (1999) Descriptive epidemiology of injury and illness among cruise ship passengers. *Ann Emergen Med* **33**: 67–72.
20. McCaig L (2000) *National Hospital Medical Care Survey: 1998 Emergency Department Summary*. Advance Data NCHS 313, National Center for Health Statistics, Hyattsville, MD.

Additional resources

Useful addresses

American College of Emergency Physicians Section of Cruise Ship and Maritime Medicine
PO Box 619911
Dallas, TX 75261-9911, USA
+1 800 798 1822
www.acep.org

American Society of Tropical Medicine and Hygiene 60 Revere Drive, Suite 500
Northbrook, IL 60062, USA
+1 847 4809592
www.astmh.org

Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30333, USA
+1 800 311 1345, 404 639 3534
Traveler's Hotline 877 394 8747
www.cdc.gov

Health Canada
AL 0904A
Ottawa, K1A 0K9, Canada
+1 613 957 2991
www.hc-sc.gc.ca

International Association for Medical Assistance to Travellers
Regal Road
Guelph, Ontario N1K1B5, Canada
+1 519 836 0102
www.iamat@sentex.net

International Association for Medical Assistance to Travellers (USA)
417 Center Street
Lewiston, NY 14092, USA
+1 716 754 4883

International Council of Cruise Lines
2111 Wilson Boulevard 8th Floor
Arlington, VA 22201, USA
+1 703 522 8463
www.iccl.org

International Maritime Health Association Italielei 51
B-2000 Antwerp, Belgium
+32 3 229 07 76
www.semm.org/IMHA/IMHA.html

International Maritime Organization
4 Albert Embankment
London SE1 7SR, UK
+44 020 7735 7611
www.imo.org

International Society of Travel Medicine
PO Box 871089
Stone Mountain, GA 30087-0028, USA
+1 770736 6732
www.istm.org

Pan American Health Organization (WHO Regional Office)
525 23rd Street, NW
Washington, DC 20037, USA
+1 202 974 3000
US State Department Travel Warnings
+1 202 647 5225
http://travel.state.gov/travel__warnings.html

Wilderness Medical Society
3595 E. Fountain Blvd. Suite A1
Colorado Springs, CO 80910, USA
+1 719 572 9255
www.wms.org

World Health Organization
Avenue Appia 20
1211 Geneva 27, Switzerland
+41 22 791 21 11
www.who.ch

Health Care Guidelines for Cruise Ship Medical Facilities (Reproduced from [1] with permission)

The American College of Emergency Physicians believes that appropriate emergency care and healthcare maintenance for passengers and crew members aboard ships sailing in international waters are desirable. The cruise ship industry and its medical departments should retain medical personnel who can:

- Provide quality maritime medical care for passengers and crew members aboard cruise ships.
- Initiate appropriate stabilization, diagnostic and therapeutic maneuvers for the critically ill or medically unstable patient.
- Support, comfort and care for patients on board ship.
- Assist, in conjunction with the cruise line, the medical evacuation of patients in a timely fashion when appropriate.

Health Care Guidelines for Cruise Ship Medical Facilities: Policy Resource and Education Paper (PREP)

The specific medical needs of a cruise ship are dependent on variables such as ship size, itinerary, patient (passenger and crew) demographics, number of medical facility visits, etc. These factors will modify the applicability of these guidelines, especially with regards to staffing, medical equipment and the ship's formulary.

Medical care on cruise ships would be enhanced by ensuring that cruise ships have:

1 A ship medical centre with medical staff (physicians and registered nurses) on call 24 h a day, examination and treatment areas, and an inpatient medical holding unit adequate for the size of the ship.

A medical centre with adequate space for diagnosis and treatment of passengers and crew members with 360° patient accessibility around all beds/stretchers and adequate space for storage.

- One examination/stabilisation room per ship
- One intensive care room per ship
- Minimum number of inpatient beds: 1 bed per 1,000 passengers and crew
- Isolation room or the capability to provide isolation of patients
- Access by wheelchair and stretcher
- Wheelchair-accessible toilet on all new builds delivered after 1 January 1997

2 Physicians with:

- Current medical licensure
- 3 years of post-medical school clinical practice
- Board certification in: emergency medicine, family practice, internal medicine, or general practice and emergency medicine experience
- Competent skill level in advanced life support and cardiac care
- Minor surgical skill (i.e. suturing, incision and drainage of abscesses, etc.)

3 A medical staff:

- Fluent in the official language of the cruise line
- Fluent in English
- Maintaining well-organised and legible standardised documentation of all medical care.

4 Emergency medical equipment, medications and procedures:

Equipment

- Airway equipment: bag valve mask, pocket mask, endotracheal tubes, stylet, lubricant, vasoconstrictor, portable suction equipment
- Cardiac monitor and back-up monitor (total of two)
- Defibrillator (portable), total of two, one of which may be a semi-automatic defibrillator
- External cardiac pacing capability
- Electrocardiograph
- Infusion pump
- Pulse oximeter
- Nebuliser
- Automatic or manual respiratory support equipment
- Oxygen (including portable oxygen)
- Wheelchair
- Stair chair and stretcher
- Refrigerator/freezer
- Long and short back boards, cervical spine immobilisation equipment
- Trauma cart supplies

Medications

- Emergency/code cart medications and supplies for management of common medical emergencies that include sufficient quantities of advanced life support medications for the management of two complex cardiac arrests

Procedures

- Medical operations manual as required by International Safety Management Code requirements
- Medical staff orientation to the medical centre
- Maintenance for all medical equipment
- Code team trained and updated regularly
- Mock codes as recommended by the ship's physician
- Emergency preparedness plan as required by the International Safety Management Code.

5 Basic laboratory and X-ray capabilities:

- Haemoglobin/haematocrit estimations, urinalysis, pregnancy test, blood glucose (all test procedures with a quality control program as recommended by the manufacturer)

(*Modern cruise ships are now often equipped with a desktop laboratory and diagnostic kits that allow the medical staff to perform complete blood counts, blood chemistry testing, basic blood typing and cardiac enzyme evaluations*)

- X-ray machine for new builds delivered after 1 January 1997.

6 A request for passengers to provide information regarding any personal medical conditions that may require attention aboard ship.

7 A health, hygiene and safety programme for medical personnel that includes an annual tuberculosis screening programme.

Section V
Environmental hazards of travel

Chapter 20 Travel-related injury

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Introduction

Inherent in the desire to travel is the desire for new experience. The exposure to different surroundings and the excitement of the change itself yield the traveller to risks of unfamiliar proportion. All too often a journey ends prematurely as the result of injury. This chapter provides an overview of current knowledge concerning travel-related injury, and provides a broad framework that can be used to minimise actively the occurrence and impact of injury.

Epidemiology

To analyse the epidemiology of travel-related injury one looks at morbidity and mortality studies to define the overall population status.

In the formative study by Hargarten [1] of the deaths of 2,463 American travellers over a 10-year period, it was found that 24% were caused by injury. Of these, motor vehicle crashes were the most common (27%), followed by drowning (16%). In an analysis of cases transported back to the United States by emergency medical air transport over a 3-year period [2], 44% were due to injury. More than half of these were the result of motor vehicle accidents. Studies from other countries echo these data. The deaths of Scottish citizens abroad from associated injury have been measured at 21% [3]. The deaths of Australians overseas have been quantified [4]: 35% cardiovascular, 18% injury and 2% infection. The deaths due to injury were mainly the result of motor vehicle accidents. Within Australia, the deaths of visitors to the state of Victoria were found to be due to cardiovascular disease (47%) and injury (19%) [5]. The injuries were mainly motor vehicle accidents; other causes were drowning, suicide or multi-traumatic. Of overseas visitors admitted to a hospital in the Australian state of Queensland over a 12-month period [6], the main reason for admission was for injury and poisoning (38%). The other reasons were cardiovascular (12%), gastrointestinal (10%) and genitourinary (9%).

These studies present a tantalising glimpse of the magnitude of travel-related injury, but unfortunately they are at best fragmented. There are many surveys of health service utilisation that indicate that injury is a common event while travelling [7]; however, the information is of an uncontrolled nature, and as such only offers snapshot views of morbidity and mortality. We await the larger-scale controlled studies that will take into account the various exposure indices, such as length of stay or activities undertaken, and individual indices, such as age or sex. These types of study, when combined with available population statistics, will allow injury rate calculation and a more in-depth account of injury mechanism.

As a consequence of the diversity of exposure and accident types, the epidemiology is poorly defined. This is not too dissimilar to all other areas of injury research, and indeed many areas of public health. There are difficulties in the definitions of both cases and injury types. Surveillance is fragmented, or even absent. Interventional studies are rare indeed.

In order to attempt to analyse travel-related injury it is necessary to use a risk-based approach. This involves risk identification and risk management. Risk can be sourced from the environment that the travellers are in, through to the individuals themselves. An individual has many variables, such as age and sex, activities planned, behaviours adopted, precautions taken and, most importantly, what their particular perception of risk is. The environment poses an infinite array of risks.

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Case-based approach

As with other areas of public health where the data are limited, it is desirable to review issues on a case study format. To illustrate the case-by-case nature of injury, let us consider the following actual cases:

1 A tourist awaits her bag at the luggage carousel at an airport. The bag weighs in excess of 30 kg. The ergonomics of the situation are very poor: a moving heavy load at shin height, the tourist with a bent back and an outstretched arm. A wrenched shoulder and an acute lumbar disc prolapse result. Conservative management of the back injury fails and spinal surgery is required.

2 A group of travellers on an organised coach tour elect to participate in an optional excursion canyoning with a suggested local operator. All are complete novices to the sport, but the activity includes guides and equipment. While they are deep in a ravine, heavy rains upstream cause flash flooding, with resulting confusion and chaos; 18 young tourists drown.

3 On a quiet river in Africa, canoeing close to shore, a tourist is unseated when a hippopotamus overturns the craft. In the resulting confusion the hippopotamus attacks and bites the tourist, killing him.

4 A couple of experienced divers are diving while on holiday with a small group operator. The dive concludes, and the boat returns to port. It is noted that the two divers are missing. Extensive search and rescue only finds fragments of diving equipment; the divers are never found.

5 A middle-aged tourist on a self-drive tour stops to climb a look-out. While descending he loses his footing and falls some 15 m. This results in serious head injuries and multiple fractures. The rescue response takes over 2 hours to extract him and transport him to the nearest hospital.

6 Honeymooners on a self-directed trip decide on a white water rafting day tour. All safety equipment and guides are included. While passing through some rapids, one of the pair falls from the craft. Tossed about in the water, she strikes her shoulder heavily against some rocks, fracturing the humerus. A quick extraction from the water by the vigilant guide prevents further mishap.

7 Resting outside the clubhouse of a golf club, a visitor is struck on the head by a misdirected golf ball. The resultant skull fracture and loss of consciousness requires him to spend a few days in hospital and shortens his holiday.

The lesson from these cases is that travel-related injury is heavily reliant on individual and activity-related factors. From each of these cases it can be seen that there are a multitude of factors involved. There are two ways to view an accident: that it is the individual who is at fault and that they should change behaviour, or that the accident occurred as a systematic error and not as a single point event. Injury prevention research is directing attention away from the individual to the organisational level. Let us consider the issues involved in the above case examples.

1 The tourist with the back injury could be blamed for packing such a heavy suitcase and for not lifting it correctly. But what of the design of the luggage carousel? It presents the suitcase at a height too low for correct lifting, and it is also moving. Even consider the design of the suitcase. Why are they made so big and cumbersome?

2 Of the 18 deaths following a canyoning adventure, it could be said that inexperience in the participants was a major factor, and that the activity was dangerous and they were taking a risk. Were they warned of this risk? Why was the activity allowed in such dangerous weather conditions? Were there warning systems in place to signal the guides of impending flooding? Was there a disaster plan? The legal issues around this case could indicate corporate negligence, involving both the overall tour organiser and the activity organiser.

3 Hippos are dangerous. Do all tourists know this? Why was an unsuspecting paddler allowed so close to one?

4 The diving case highlights the problem of lack of attention to procedures. When this case occurred the press suggested that the victims were part of a suicide pact. The inquest into the deaths found the dive operator negligent in not following correct occupational health and safety procedures.

5 Falls involving tourists are a frequent occurrence. Are we to blame the tourist for the fall because he was wearing inappropriate footwear, was fatigued or was unfit? What of the walkway itself: what type of surface was it, were the steps well placed, were the safety rails adequate? The rescue response was poor and required review.

6 White water rafting is often considered by tourists to be safe. How common are such events? Are tourists adequately warned of these? The rescue by the guide demonstrates a high level of competence.

7 There is a real danger around a golf course of being struck by an errant ball. Whose responsibility is it? The person struck, the hitter or the course management? Was any attempt made to minimise the occurrence of such an event, such as protective screens or relocation of the rest area?

All these cases could be examined further. Examination can be systemised by the use of a framework: one that is particularly helpful is that illustrated in Figure 20.1. The terms used in the framework are easily explained.

- The context refers to the setting of the tourist activity, the environment and the individual.
- The identification of the risks requires a review of the available data, be that from morbidity and mortality data,

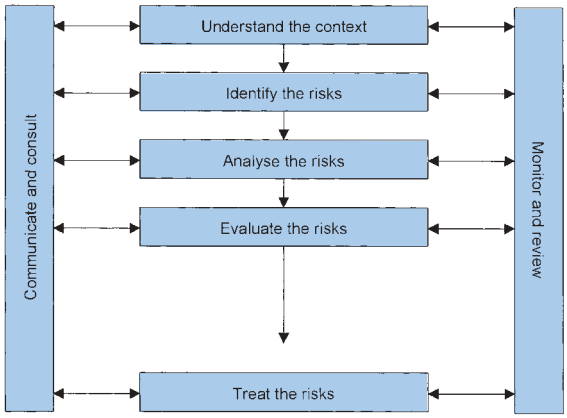

Figure 20.1 Australian/New Zealand standard framework for risk management. See text for explanation.

case reports, service utilisation patterns or other available sources.

- To analyse the risks is to determine the mechanism of injury. What actually happened?
- An evaluation of the risk requires an appreciation of the frequency of that particular event, whether it has a high impact, and whether there is a simple solution.
- Treating the risk could involve a multitude of methods, from educational activities to engineering modifications.
- Most important is the continued monitoring and review of the whole process, as with a disease surveillance system.
- Communication and consultation are also vital—with the individual, the tourist operator and any other relevant organisation.

The systematic analysis of each of the above cases would piece together what went wrong, identifying risks and areas that could be modified to reduce this risk.

Using the framework for case analysis starts with the analysis of existing morbidity and mortality data, from which is determined the pattern of injury. Injury mechanism is then determined, pertaining both to the individual and to the environment. From here, assumptions can be made on the causative factors for injury. A safety profile is then developed, so that reasonable action for risk reduction may be undertaken. To appreciate the process of developing strategies for specific problems relating to adverse health outcomes in the tourist setting, beach-related trauma and motor vehicle accidents will be considered in more detail.

Beach-related trauma

A visit to the beach is a common tourist activity. Consider this case study analysed using the risk management framework.

Risk identification and analysis

Two studies carried out on an Australian beach found the following [8, 9]:

- lacerations were very common, mostly to the feet but many to the head
- drownings, near-drownings, ocean rescues, major limb fractures, joint dislocations, sunburn and various marine bites were occurring
- the causes of injuries included rocks, litter and surfcraft
- there were falls from walkways
- individuals were being caught in strong sea currents.

Utilising available beach usage data, a rate of injury was calculated at 100 per 100,000. This means that for every 1,000 beach users, one person can expect to have to visit a doctor after the beach trip.

To add to the data from these studies, information related to various specific activities, such as drowning, ocean rescues, snorkelling and surfing, can be analysed. Drownings have been extensively studied [10] along the same region as the beach studies. This study found that the following features are common: male sex, consumption of alcohol and swimming alone outside patrolled beach areas. Ocean rescues occur more frequently outside patrolled areas, involve overseas visitors disproportionately, and occur more frequently in people who live more than 50 km from the coast [11]. A study of mortality reports of people who died while snorkelling [12] indicated a disproportionate number of overseas visitors, a lack of wearing of flippers and the absence of snorkelling with a 'buddy'. Surfing studies have indicated that collision with the rider's own board is a common source of laceration [8].

Risk evaluation

High-impact risks ('nasty events') include those that result in death or hospitalisation. Frequent events are falls and cut feet. Simple preventive measures include using safety equipment that is already available, appropriate footwear, sunscreen and safety rails.

Treatment of risk

This could include the following.

- Environmental factors – water currents, manmade structures such as walkways, natural hazards such as vegetation.
- Litter – control methods, collection, individual behaviours such as litter disposal and the wearing of footwear, fines for errant behaviour.
- Surfcraft – activity zones, board design, nose tips, helmets, education.

• Human factors – alcohol, overexertion, behavioural (attitude, bravado), lack of skills, education, protective apparel.
• Service provision – formal team approach, incorporation of beach safety into the planning phase of coastal developments, training, lifesavers, search and rescue, health infrastructure, first aid, emergency location systems, surveillance of service utilisation.
• Location – beach access, effective beach user traffic control, designation of water activity zones.
• Advertising – on a large scale by public education in the press, at the airport, on the airline arrival video, in hotel brochures; or locally by the use of appropriate signs, delineating hazards.
• Education – of beach users, on hazard identification, beach behaviour and how to swim.

Communication and consultation

In Australia, the bodies responsible for the management of the beach area include local management bodies (foreshore committee), regional authorities (shire, state government departments), national authorities (federal government), service providers (Surf Life Saving Association, medical colleges, ambulance service), regulatory bodies (consumer affairs). In response to a spate of beach drownings, a National Water Safety Council was formed and developed a national water safety strategy. Its success requires local action on the recommendations.

Monitoring and review

If events and the circumstances of their occurrence are recorded, it is possible to determine trends in incidents and whether interventions have been effective. Sadly this is not occurring for beach-related injuries, nor is it on the agenda. It is essential for the refinement of beach injury control.

Motor vehicle accidents

Motor vehicle accidents emerge consistently as the most common cause of tourist death due to injury [13]. Let us consider an analysis of travel-related motor vehicle accidents in the context of the Australian state of Queensland, where a recent volume of research has been conducted.

Risk identification

Using data from road crash investigations, hospital records and insurance claims, it was determined that over a 5-year period there were 39 fatalities and 397 hospitalisations of international drivers in Queensland [14]. Calculations of the social costs of road crashes determined that for the year 1997 these amounted to A$18 million. International visitors were more likely to be involved in head-on collisions.

Risk analysis

The factors identified as contributing to motor vehicle accidents involving tourists were disorientation, fatigue, unfamiliarity with driving conditions and omitting to wear a seatbelt [15]. Disorientation relates to the side of the road visitors drive on in their home country. Fatigue relates to the long distances travelled in Australia, compounded by jet lag and travel fatigue. The driving conditions vary: the road surface, the road signs, the presence of wildlife and other Australian nuances. Home country attitudes to alcohol use while driving and the wearing of seatbelts affect the tourist's compliance with Australian road laws. International literature confirms these factors as important sources of road accidents [16–19].

Risk evaluation

'Nasty events' need close attention; again, these are the events that lead to death or hospitalisation. Various strategies could be undertaken to minimise the risks. Increasing the use of seatbelts, minimising disorientation, tackling fatigue and increasing awareness of differences in road conditions could be included in national road safety initiatives for all road users, not just for tourists.

Treatment of risk

This could include the following.
• Advice and driver education. Pre-departure advice could consist of a discussion of the effects of medication, alcohol and jet lag on driving; the use of seatbelts; and the use of rest stops to counter fatigue. On collection of the hire vehicle there could be a screening of a video highlighting vehicle safety. A familiarisation programme of the vehicle to be hired could be conducted at the time of its collection.
• Stickers placed in the vehicle could be used to prompt the use of seatbelts. One initiative could involve engine immobilisers that cut the engine if the driver's seatbelt is not fastened.
• Hiring well-maintained vehicles with accepted safety features such as advanced braking systems and air bags. In-vehicle satellite navigation systems reduce driver distraction considerably.
• For off-road and remote driving, the supply of detailed manuals, first-aid kits and satellite locaters is sensible.
• Emergency services need to be maintained and well funded to assist in the rapid response to crashes.

• Tourists need to purchase insurance cover that will provide for medical assistance and rescue.

Communication and consultation

In the Queensland case, a state government inquiry into the international road crash issue was held. This forum allowed medical specialists, accident researchers, tour operators, and representatives from the insurance industry and government departments of transport and tourism to discuss issues involving international visitors and road safety. Continued dialogue between these parties could lead to the development and implementation of many safety initiatives. A review was published after the forum [20].

Monitoring and review

Ongoing monitoring of the situation can be conducted by accident research centres, analysing crash reports, coroners' reports, road mortality and morbidity data, and insurance claims.

Concluding remarks

Use of the management framework allows for an integrated approach to risk management. It relies on best-available evidence-based actions, allows input from the various stakeholders, from the tourist to the operator, and can be nationally coordinated with policy support. What it demonstrates is the multifaceted causation of injuries and how a systematic approach can lead to rational and evidence-based responses.

Areas of action that can be taken when considering travel-related injury are discussed below.

Travel health physician

The basic provision of structured injury prevention and risk minimisation advice is paramount; this includes the determination of the risks apparent from a detailed account of the traveller's proposed itinerary and any particular health conditions that they may have.

• Highlight the consequences of risk exposure.

• Strengthen the advice with brief, to the point, written material.

• Advise pertinent preventative actions: for example, travel with an organised tour group if undertaking adventure activities (with a reputable organisation, standards would be expected to be higher, and risks correspondingly reduced); hire a car and a driver; wear protective equipment; do not mix alcohol with physical activities; seek local safety information, e.g. fire escapes, safe areas to swim.

• Explain the value of travel insurance, as medical evacuations are expensive and access to high-quality health services is often limited, due to language, knowledge, distance from centres, and infrastructure deficiency.

Travel health physicians are in an ideal position to continue research into specific travel injury risks. Much information is needed on the incidence, rate and causation of travel-related injury, as is more information on effective proven strategies to reduce the injury caseload.

Tourism industry

This includes all levels of the industry, from the individual operator to the regional authorities. Guidelines for the risk management of a tourist activity or a tourist site development should minimise risk at the planning stage. There must be an assessment of the impact of the development on safety. Safety plans need to be prepared, specifying safety resources to match predicted usage patterns, identifying problem areas and controlling the risks. Users and service providers need education about risks and preventive strategies. Litigious exposure should be minimised.

There is a requirement for the development of standards of operation that include safety mapping, entailing the audit of safety risks, management of these risks and maintenance of an injury register. This entails the development of a safety plan and direct action on it. All too often the best intentions still lead to inactivity. Incidents need investigating, which is certainly a process that occurs in many other industries, from which many important lessons can be learned for refinement of risk control. Management of legal risk is essential, and legal security is part of a complete risk management programme [21] that is often referred to as loss control. Indeed, changes in insurance premiums can often produce changes in attitude and actions of errant operators: as the number of claims increase, so does the premium.

Insurance industry

Travel insurance packages must provide broader cover. The 'small print' needs to be large, so that travellers know what is and is not covered, and can then make an informed decision about purchasing the appropriate policy.

Older travellers are increasing in number and, more than any other group, need insurance cover. The habit of not covering existing medical conditions is nonsensical. For example, an 80-year-old man with ischaemic heart disease is likely to experience a cardiac event, so he should be encouraged to cover such an event and should be able to obtain a reasonably priced policy to do so.

The adventure traveller needs specialised cover that includes the activities to be undertaken. It is all too easy to say 'rock climbing not included' but, when that is the purpose of the trip, the insurance broker must be able to provide an adjusted policy that does cover rock climbing. The exclusion of motor cycle riding (either in defined areas or as a blanket clause) by a number of policies may act as a deterrent for many travelers – that is, if they are aware of the exclusion. But what of the traveller who has no other option to a motorcycle as a means of transport? There should be a policy variation to cover this situation.

Governments

Many countries rely heavily on tourism for revenue; in Australia, for example, tourism is a major industry employing over 6.9% of the workforce and generating over A$46.9 billion [22]. It would therefore seem obvious that it is very important to protect the industry by the provision of adequate health and safety management. This is not the case. It seems absurd that health and safety in tourism settings are not regarded with as much importance as they are in the mining industry. Government departments need to focus on health and safety management in tourism, with legislation providing a backbone for operation. This would include the enforcement of codes of conduct and the prosecution of unsafe practices. Planning is necessary for the designation of specified activity zones. With each new tourist area developed, consideration of the safety implications is required. Placing a resort in an isolated area next to a serious hazard, for example a beach that is unsafe for swimming, is a reason for concern, raising questions about adequate monitoring of water activities and how serious mishaps are to be managed. The service infrastructure is vital in such cases. Not only does this cover the provision of adequate transport, but it should also provide for appropriate rescue services, evacuation services, primary treatment facilities, and so on.

Summary

Injuries associated with travel are very common but the exact nature and incidence is not precisely known; however, to appreciate the risks of a specific activity, it is possible to analyse it with a generic framework. Injury prevention requires a systems approach, attempting to identify process errors, as there are usually a multitude of causative factors for each particular injury. It must be remembered that in cases of injury it is all too easy to blame the individual, when very often it is not the individual's fault.

References

1. Hargarten S *et al.* (1991) Overseas fatalities of United States citizen travellers: an analysis of deaths related to international travel. *Ann Emergen Med* **20**: 622–626.
2. Hargarten S and Bouc G (1993) Emergency air medical transport of US citizen tourists: 1988 to 1990. *Air Med J* **12**: 398–402.
3. Paixao M *et al.* (1991) What do Scots die from abroad? *Scot Med J* **36**: 114–116.
4. Prociv P (1995) Deaths of Australian travellers overseas. *Med J Australia* **163**: 27–30.
5. Grenfell R *et al.* (1997) Mortality of visitors to Victoria Australia. In: Proceedings of an ISTM conference, Geneva.
6. Nicol J *et al.* (1996) Tourists as inpatients in queensland regional hospitals. *Aust Health Rev* **19**(4): 55–72.
7. Bewes P (1993) Trauma and accidents: practical aspects of the prevention and management of trauma associated with travel. *Br Med Bull* **49**: 454–464.
8. Grenfell R and Ross K (1992) How dangerous is that visit to the beach? A pilot study of beach injuries. *Aust Fam Physician* **23**: 1145–1148.
9. Grenfell R (1996) Beach related injuries. *Med J Australia* **166**: 390.
10. Manolios N and Mackie I (1988) Drowning and near-drowning on Australian beaches patrolled by life-savers: a 10 year study, 1973–83. *Med J Australia* **148**: 165–171.
11. Short A *et al.* (1991) A three year study into the circumstances behind surf based rescues. NSW Beach Safety Program Report 91. Sydney Coastal Studies Unit, University of Sydney.
12. Edmonds C and Walker D (1999) Snorkelling deaths in Australia, 1987–1996. *Med J Australia* **171**: 591–594.
13. Wilks J (1999) International tourists, motor vehicles and road safety. *J Travel Med* **6**: 115–121.
14. Wilks J and Watson B (1998) Road safety and international visitors in Australia: looking beyond the tip of the iceberg. *Travel Med Int* **16**: 194–198.
15. Wilks J and Watson B (1999) International drivers in unfamiliar surroundings: the problem of disorientation. *Travel Med Int* **17**(6): 162–167.
16. Hargarten SW (1991) International travel and motor vehicle crash deaths: the problem, risks, and prevention. *Travel Med Int* **9**: 106–110.
17. Petridou E *et al.* (1997) Epidemiology of road traffic accidents during pleasure travelling: the evidence from the island of Crete. *Accident Anal Prev* **29**: 687–693.
18. Petridou E *et al.* (1999) Are traffic injuries disproportionately more common among tourists in Greece? Struggling with incomplete data. *Accident Anal Prev* **31**: 611–615.
19. Carey MJ and Aitken ME (1996) Motorbike injuries in Bermuda: a risk for tourists. *Ann Emergen Med* **28**: 424–429.
20. Wilks J *et al.* (1999) *International Visitors and Road Safety in Australia: A Status Report*. Australian Transport Safety Bureau, Canberra.
21. Grenfell RD and Ranson D (1997) Tourism and recreational injuries. *J Law Med* **4**.
22. Department of Industry, Science and Tourism (1996) *Impact: Tourism Facts*. DIST, Canberra.

Chapter 21 International assistance and repatriation

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Introduction

The increase in foreign travel, the rise in holidays to exotic locations and the enthusiasm for adventure holidays has led to an increase in the requirements for medical repatriation services in the past decade. An ageing population with increased disposable income is expected to lead to a rise in the number of air ambulance transfers each year. People who fall ill or have an accident abroad can be repatriated to the UK by a number of methods.

- They may organise their own transport, either alone or with an escort.
- They may travel on a scheduled flight with a doctor or nurse escort.
- They may require an air ambulance on a scheduled flight or chartered aircraft.

In the region of 3,000 patients a year are repatriated on scheduled airline services with a nurse escort and there are approximately 900–1,000 air ambulance transfers into the UK per annum [1]. In Europe, the German Air Rescue service has shown a steady increase in the number of flights, from 322 in 1976, to 704 in 1983 to 1,468 in 1993 [2, 3] and more than 38,000 missions in 2011.

This chapter will focus on the logistics and problems associated with air ambulance transfers.

Medical transfers

The medical transfer of a patient can be designated as primary or secondary: primary transfer is from the scene of injury or illness to the initial treating hospital; secondary transfer is the movement of a patient from one hospital to another for medical or social reasons. All cases of medical repatriation should be deemed secondary transfers, although some may be undertaken with a degree of urgency and without definitive treatment having been performed. In the majority of cases, patients will have been treated in countries in which the healthcare facilities are of a good standard. In these situations transfer usually occurs once the patient has been fully stabilised and all urgent therapy initiated. However, these patients may still require a high degree of supportive therapy, including intensive care. In countries where the healthcare resources are felt to be inadequate, the patient may be transferred back to the UK at an earlier stage of the illness. In some cases the air ambulance team may need to institute resuscitative and supportive procedures before the patient is deemed fit to fly. In the rare situation where medical care is completely inadequate or unavailable, a primary rescue flight may need to be undertaken. Occasionally the patient may be transferred locally to a region or country that can provide the required resources. If communications are difficult and the clinical situation is not clear, a doctor may be flown out to assess the patient and decide if transfer is required.

All transfers place the patient at some risk, and poorly conducted transfers have been shown to be detrimental to outcome [4–6]. The risk of transfer should be balanced against the risk of deterioration in a suboptimal environment. For an escorted scheduled flight, the patient's condition should be unlikely to deteriorate, not contagious, not disturbing to other passengers, require minimum nursing or medical care and the patient should be able to travel seated. If the patient requires high-dependency or intensive care or needs to be transported on a stretcher, an air ambulance transfer should be performed either via a scheduled carrier or in a chartered jet. The use of a scheduled flight or chartered aircraft will depend on the clinical condition, the distance to travel, the availability of flights and the conditions stipulated by the carrier. Approximately 90% of stretcher cases are transported on small chartered aircraft [2].

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Organisation of repatriation services

Air ambulance flights are expensive. Prices quoted vary from £5,000 to £19,000 to return from Mediterranean countries, £35,000 to £50,000 from Africa and £60,000 from the US. However, these prices should be balanced against the cost of healthcare itself, particularly the cost abroad of major procedures and intensive care therapy. Fortunately, most people carry health insurance while travelling. On each insurance document is a telephone number to contact in case of a problem. This is the number of an assistance company, the first point of contact the patient or relative makes with the repatriation services. There are approximately 20 major assistance companies in the UK. They provide a 24-hour telephone service and help in organising logistical support for anyone with a problem abroad. In the event of an air ambulance being required, a quarter of the assistance companies provide their own in-house service; the remainder will subcontract to a company that supplies repatriation services. There are four major repatriation service providers within the UK, and numerous smaller operators. There are also European air ambulance companies available, some of which are subsidised by governmental ambulance systems.

Deciding when to repatriate a patient

The decision to repatriate depends on medical, social and political factors (Table 21.1). The assistance company will have a medical director – either a consultant or general practitioner with experience in repatriation. It is the duty of the medical director, or the deputy, to liaise with the treating and the receiving hospital medical staff. If an air ambulance company is involved, they will have their own medical staff in the communication loop (Figure 21.1), with separate responsibility for care of the patient during transport. In an ideal world there would be a complete assessment and discussion of the case between all medical parties involved and the final decision to repatriate would be made at consultant level or the equivalent (Table 21.2). However, in reality many problems are encountered. There are difficulties in communication and language, and in some cases disagreement on patient management. Social factors also come into play. There is a question of finance: will the insurance cover the cost of transport or will the repatriation be undertaken privately? If privately, financial securities are required before initiation of an air, and this causes delays. The patient's expectations of being repatriated may not agree with the insurance company's views. Social reasons for repatriation can be the expectation of a long period of therapy, a language barrier, lack of nursing care, problems with diet and climate. Most patients prefer to be in a familiar environment where their family and friends are close and can provide emotional support. It is likely that the rate of recovery and the incidence of complications such as intensive care psychosis may be affected by factors that reduce communication between patient and medical staff. It is hard to motivate a patient who cannot understand what you are saying.

Table 21.1 Factors involved in making the decision to repatriate

- Healthcare facilities at the treating unit
- Patient's condition and progress
- Expected duration of treatment and level of expertise available
- Potential detrimental effects of transport
- Potential risk to the patient if not transferred
- Availability of aircraft
- Availability of beds within UK, particularly intensive care beds

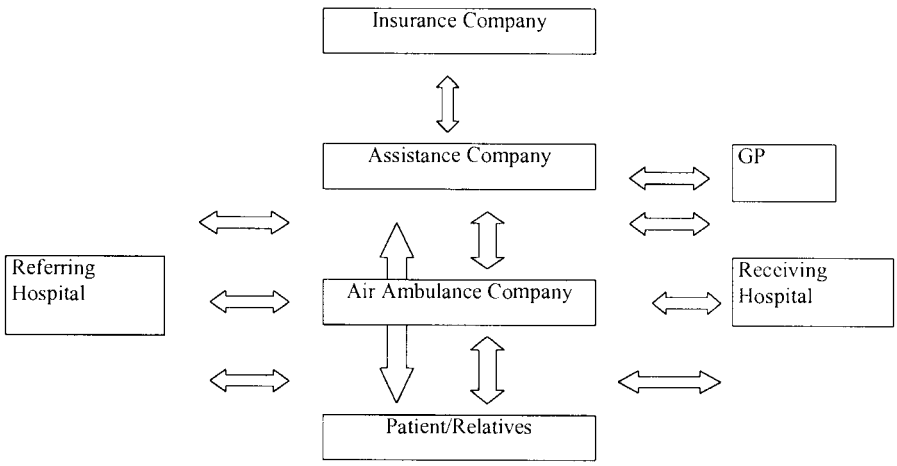

Figure 21.1 Communication loop involved in the decision to transfer a patient.

Table 21.2 People involved in making the decision to repatriate

- Referring doctor
- Assistance company doctor
- Receiving doctor
- Air ambulance company
- Air ambulance escorting doctor and nurse
- General practitioner in the UK
- Relatives, next of kin or legal guardian

Table 21.3 Physical changes associated with increasing altitude

Altitude (feet)	Pressure (kPa)	Gas volume (litres)	P_AO_2 breathing air (kPa)
0	101	1	14
5,000 (1,500)	84	1.2	10
8,000 (2,400)	75	1.35	8.5
10,000 (3,000)	70	1.44	8.4
20,000 (6,000)	46	2	5
38,000 (11,600)	21	5	NA

Values in parentheses are metres.
NA = not applicable.

Physics and physiology of air travel

The density of the atmosphere decreases exponentially with altitude. With increasing altitude there is a drop in the molecular concentration of gas particles, expansion of gas volume and a reduction in pressure (Table 21.3). These physical changes can lead to alterations in the physiological status of patients during aeromedical repatriations [8].

Pressure changes

Air ambulance flights are carried out in turboprop or subsonic jet aircraft that fly at altitudes of between 25,000 and 40,000 feet. To allow the occupants to breathe air and move freely within the cabin, the aircraft is pressurised. There are a variety of terms used to describe aircraft cabin pressure. The absolute cabin pressure is the internal pressure within the cabin itself. Atmospheric pressure is the outside atmospheric pressure at the altitude at which the aircraft is flying. The cabin differential pressure is the difference between the external and internal pressures:

Cabin differential pressure = cabin pressure
– atmospheric pressure.

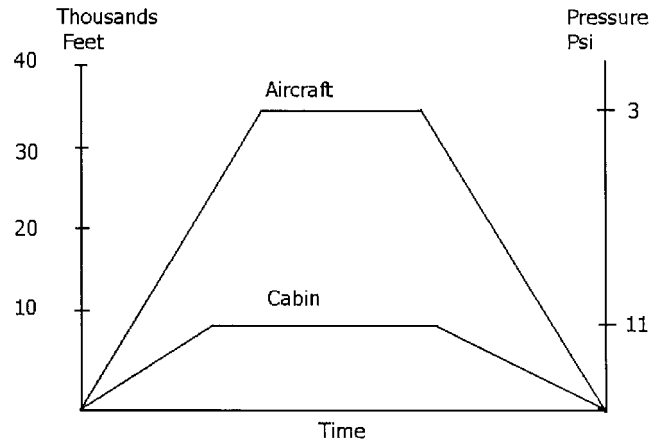

Figure 21.2 Cabin versus aircraft altitude.

During ascent the pressure within the cabin falls until it reaches a predetermined minimum absolute cabin pressure, usually described in terms of equivalent cabin altitude (Figure 21.2). As the aircraft climbs further, the cabin altitude is maintained and a cabin differential pressure results between the internal cabin pressure and the external atmospheric pressure. The cabin differential pressure reaches a maximum at the operational ceiling of the aircraft. The aircrew can adjust the cabin differential pressure during flight. If the aircraft is flying below its operational ceiling, increasing the cabin differential to its maximum will maintain a low cabin altitude and will minimise the effects of altitude-related environmental changes. Air ambulance cabin altitudes range from 6,000 to 8,000 feet (1,800–2,400 m); the absolute cabin pressure therefore ranges between 81 kPa (609 mmHg, 11.8 psi) to 72 kPa (543 mmHg, 10.5 psi).

The most important features of this pressure change that affect patient physiology during ascent are as follows.

1 The rate of change in cabin pressure. This determines the rate of volume change within gas-filled cavities. It is described in terms of rate of climb or descent. Ascent is usually better tolerated than descent and in commercial aircraft the rate of descent of cabin altitude is kept below 300 feet (90 m) per minute, which is less that the actual rate of descent of the aircraft.

2 The end cabin altitude (maximum 8,000 feet [2,400 m]), which determines total volume of gas expansion and the drop in partial pressure of oxygen.

3 The final aircraft altitude, which determines the degree to which cabin pressure must fall and also the effects of accidental loss of cabin pressure (see below).

Hypobaric hypoxia

During ascent through the atmosphere there is a fall in density of air and a reduction in the molecular concentration

of oxygen. This in turn leads to a fall in the partial pressure of oxygen within the lung, and hence the blood. At 8,000 feet (2,400 m), atmospheric pressure is reduced by 25%, from 101 kPa to 75 kPa. The alveolar partial pressure of oxygen (P_AO_2) drops from 14 kPa to 8.5 kPa. There is minimal effect on the physiology of fit individuals, other than some minor reversible deterioration in mental performance for novel tasks, detected on psychometric tests. The patient's susceptibility to hypoxia depends on the underlying cardiopulmonary function, intercurrent disease, physical activity and metabolic rate. The drop in partial pressure of oxygen at cabin altitudes of 8,000 feet (2,400 m) is sufficient to cause tissue hypoxia and the development of symptoms in patients with reduced cardiopulmonary reserve. The physiological response to this hypoxia is to increase ventilation, which leads to a reduction in alveolar carbon dioxide and a rise in alveolar oxygen tension. This is explained by the simplified alveolar gas equation:

$$P_AO_2 = P_IO_2 - P_ACO_2/RQ$$

where P_AO_2 is the alveolar oxygen tension, P_IO_2 is the tracheal oxygen tension, P_ACO_2 is the alveolar carbon dioxide tension and RQ is the respiratory quotient. In extreme cases, the degree of hyperventilation and hypocapnia can itself induce a separate group of symptoms.

Gas expansion

Boyle's law states that the volume of a gas is inversely proportional to its absolute pressure; therefore, as atmospheric pressure falls with ascent, gas expands (Table 21.3). In the pressurised aircraft, cabin ascent to an altitude of 8,000 feet (2,400 m) leads to gas volume increasing by 35%. This gas expansion can affect the gas-filled body cavities, depending on the degree with which they communicate with the external environment. The lungs, middle ear, paranasal sinuses and the gastrointestinal tract are all potential problem areas. In a fit individual there are few problems with this degree of gas expansion, other than mild middle ear discomfort. However, certain conditions may become significantly worse and even life threatening with this change in volume. Patients with pneumothoracies, pneumocephalus, severe bowel distension or obstructed middle ears should be taken to altitude with caution.

Acceleration/Deceleration

During take-off and landing, patients laying flat maybe exposed to forces of acceleration in the longitudinal (G_z) plane of the body. Acceleration describes the rate of change of velocity of an object and can be positive ($+G_z$) or negative, sometimes described as deceleration ($-G_z$). In aviation, acceleration is expressed as multiples of the force of acceleration exerted on a body by gravity (g) which is equal to 9.8 m/s^2:

$$G = \text{applied acceleration}/g.$$

The effects of G on the body depend on duration and direction. Short- or intermediate-duration forces are those associated with an abrupt deceleration, such as vehicle crashes. Long duration accelerations of more than 2 s occur mainly in military aircraft. In commercial aircraft, linear acceleration seldom reaches magnitudes of any significance, especially in the seated patient. The horizontal patient is unlikely to experience forces greater than $1–2 + G_z$ on take-off in a small subsonic jet. In the fit volunteer, a force of $4–6 + G_z$ is required to experience grey-out (loss of peripheral vision), black-out (total loss of vision) and G-LOC (G-related loss of consciousness). These are manifestations of reduced perfusion of the retina and brain as a result of the effects of hydrostatic forces on the cardiovascular system. There is also a progressive fall in mean arterial pressure at the level of the heart over 6–12 s, due to a decrease in peripheral vascular resistance and reduction of cardiac return. A compensatory reflex tachycardia and vasoconstriction then occurs in response to reduced pressure in the carotid sinus.

The critically ill patient may be volume depleted, vasodilated, possess a poor myocardium and have a depressed sympathetic response due to drugs or pathology. In such cases even the relatively small acceleration forces experienced combined with the 45° head-up tilt of take-off may be enough to cause a deterioration in cardiovascular function. This is easily prevented by adequate monitoring and volume loading before take-off.

Deceleration forces may cause increased blood flow to the head and neck, leading to carotid sinus distension. Reflex bradycardias and other arrhythmias have been reported in experimental situations with high G forces. Once again, it is unlikely that the forces experienced in commercial aircraft are great enough to cause these problems.

Cabin decompression

Cabin decompression is a rare event that can occur rapidly or slowly. A rapid decompression can be explosive in nature when a major defect occurs in the aircraft frame. It results in a near normal environment being quickly converted to an extreme environment, with lack of oxygen, cold and the effects of gas expansion putting the lives of patient and crew at risk. The effects of gas expansion depend on the cabin differential pressure, the altitude of the aircraft and the size

of the defect in the aircraft frame in relation to the cabin volume. The medical risks from decompression are:
- rapid loss of consciousness from hypoxia
- barotrauma to the middle ear or sinuses
- inducement of a pneumothorax
- altitude decompression sickness.

In the event of a cabin decompression, oxygen masks are automatically released and the aircraft is brought to a lower altitude. Air crew are advised to place their own oxygen mask on before helping others because of the risk of becoming incapacitated by hypoxia.

Detrimental effects of transport

The majority of medical transfers are simple escorted cases that pass off with the minimum of problems. Transporting critically ill patients is more difficult, requiring continuation of organ support and invasive monitoring. It has been shown that critical incidents, which have a detrimental effect on outcome, occur while moving these patients [8]. The environmental factors of flight mentioned in the previous section, factors associated with road transport and the logistics involved in moving the intensive care patient can all lead to adverse effects. These can be divided into major, requiring immediate intervention, and minor, leading to little disturbance to the patient. The causes can be defined as changes in physiology in response to transfer, leading to disturbed organ function and mechanical or equipment-related errors. It is difficult to stipulate when a change to physiology becomes detrimental and even harder to show a difference in outcome as a result of such a change. However, commonly used definitions of significant change are either movement from baseline vital signs by 20% or readings that fall outside the 'normal' range for the patient (Table 21.4).

Table 21.4 Defining a detrimental effect of transportation

- Deterioration in vital signs
  - Change in vital signs by more than 20% from baseline
  - Change outside 'normal' range for patient
- Mechanical, equipment or human error leading to an adverse effect on patient
  - Airway, ventilator problems
  - Handling, loading problems
  - Loss of IV access, failure of infusion system
  - Power failure
  - Failure of oxygen supply
  - Aircraft incidents

Specific hazards and their management during transport

Respiratory

- The reduced oxygen tension at altitude may lead to symptoms of hypobaric hypoxia. Arterial oxygen saturation should be monitored and supplementary oxygen administrated if indicated. If gas exchange is critical, the aircraft may have to fly at a lower altitude to maintain a sea-level cabin pressure.
- The dry atmosphere of the cabin may lead to thickening of bronchial secretion and paralysis of respiratory cilia. This can cause a deterioration in respiratory function, especially in patients whose natural humidification processes are bypassed by an artificial airway. The end result may be a spontaneously ventilating patient requiring mechanical ventilation [9]. Efforts should be made to humidify inspired gases using heat moisture exchange filters and nebulisers. Patients should receive regular chest physiotherapy, manual bagging and suction to clear secretions during transport.
- Gas expansion will increase the volume of pneumothoracies, which may lead to respiratory compromise. All pneumothoracies, or even suspected pneumothoracies, should be drained via an intercostal drain before ascent to altitude or the aircraft should maintain a sea-level cabin pressure. In trauma patients with fractured ribs there should be a low threshold for placing an intercostal drain. The use of a Heimlich valve rather than an underwater seal makes transfer simpler.
- Patients who are stable on mechanical ventilation are safe to transfer. However, caution is required if the inspired oxygen concentration is greater than 60%, lung inflation pressures are higher than 35 cmH_2O, or more than 10 cmH_2O if positive end-expiratory pressure (PEEP) is in use. In some cases, a more sophisticated ventilator than the standard transport ventilator may be required. Consideration should be made to sedating and formally ventilating patients who are on a weaning mode of ventilation. Transferring a patient is thought to set weaning back by 1 day.
- Gas-filled endotrachael cuffs increase in volume with altitude and may cause tracheal mucosal ischaemia. They should be filled with saline or their pressures monitored regularly.
- Drugs and equipment should be available for treating respiratory emergencies.

Cardiovascular

- Cardiovascular events are the leading cause of death during air travel [10].

• Any movement and stimulation of critically ill patients may cause hypertensive or hypotensive episodes [4]. There are haemodynamic changes associated with air ambulance transport, possibly due to the effects of gravitational forces and hypoxia [11]. The force of acceleration on take-off may cause a reduction in cardiac output, especially in patients who are volume depleted, vasodilated and have poor myocardial function. Adequate monitoring, including invasive arterial and central venous pressures, with institution of therapy to maintain haemodynamic stability may reduce such complications.
• Reduced inspired oxygen concentration may precipitate angina or heart failure. Oxygen should be administrated to these patients during flight.
• Despite the risks, unstable angina patients have been transferred over long distances by air. However, they require intensive therapy unit level care, adequate monitoring and sedation [12].
• Any collections of mediastinal air will enlarge, potentially causing cardiovascular compromise.
• Patients on inotropic infusions are at risk of inadvertent changes in the rate of infusions. Pumps with alarms and short, stiff infusion lines should be used. Lines should be labelled and not used for boluses.
• Non-invasive blood pressure readings have been shown to under-read systolic and over-read diastolic pressures during transport. Direct methods of blood pressure readings should be used in critically ill patients [13]. The pressure transducer should be re-zeroed at altitude.
• There is an increased risk of thromboembolic events during flight because of dehydration and immobility [14]. Support stockings may be considered and heparin prophylaxis administrated unless contraindicated.

Gastrointestinal

• Motion sickness can be treated with prophylactic antiemetics. Escorting staff should not suffer unduly from motion sickness.
• In the normal subject, gas expansion within the bowel causes little problem unless ascent is to altitudes greater than 25,000–28,000 feet (7,600–8,500 m). However, in patients with cardiorespiratory compromise and intestinal distension, even ascent up to moderate altitudes of 8,000 feet (2,400 m) can cause distress. Consideration should be given to restricting cabin altitude to less than 6,000 feet (1,800 m) in those patients with severe abdominal distension.
• Gastric distension and intestinal obstruction lead to an increased risk of aspiration of gastric contents. During transport, restricted access to the patient means that in the event of vomiting the oropharynx cannot easily be cleared. A nasogastric tube should be placed, aspirated and left on free drainage. Patients who have reduced airway protective reflexes should be considered for intubation.
• Gas expansion in the small and large bowel increases the risk of perforation in cases of severe bowel distension. There is a theoretical risk to surgical anastomoses.
• Air in the peritoneal cavity may expand and it is recommended that 10 days be allowed between abdominal surgery and transport in an aircraft not pressured to sea level.
• Ileus may be prolonged.
• Patients with abdominal or chest trauma should have no evidence of continuing intra-abdominal haemorrhage before transfer.
• Limited cleaning facilities make severe diarrhoea a major problem. Laxatives and suppositories should be avoided before travel.

Renal

• Patients requiring renal support should receive dialysis 24 h before a flight, with the objective being that the patient should have a normal electrolyte and fluid balance. Care must be taken to ensure normovolaemia.
• All critically ill patients need to be catheterised to allow monitoring of their urine output.

Neurological

• Head-injured patients should be managed to maintain cerebral perfusion pressures within a safe range: the ultimate aim being to prevent secondary brain injury. Standard guidelines for the management of head-injured patients during transport are followed [15].
• Patients with air in the skull or fractures through sinus cavities are at risk of gas expansion. This may lead to a tension pneumocephalus or the risk of bacterial meningitis. Following neurosurgery, flying other than at sea level should be delayed until computed tomograpy (CT) shows no evidence of intracranial air.
• Patients with recent subarachnoid haemorrhages should preferably have had definitive surgery if the cause of bleeding is amenable to operative intervention and if expertise is available. If surgery has not been performed, the blood pressure must be adequately monitored and controlled. Infusions of nimodipine need to be continued. If an extraventricular drain is *in situ* it should be closely monitored during flight and turned off while the patient is moved.
• Patients with a spinal cord injury must be treated as if the injury is unstable, unless cleared by an orthopaedic or neurosurgeon. They are at increased risk of requiring ventilatory assistance and need to be transferred by a doctor able to institute mechanical ventilation [9]. Spinal shock

and autonomic hyperreflexia should have been adequately treated.

Transferring patients with special needs

Paediatric/Neonatal patients

Neonatal, infant and paediatric transfers require special consideration. These transfers are complicated by the smaller size of the patient, different physiology and pathology. Specialist equipment such as a transport incubator and neonatal ventilator are required. Personnel should be skilled in neonatal and paediatric intensive care. The medical crew should include at least one doctor, either a neonatal paediatrician or paediatric anaesthetist, and a nurse with neonatal experience. Many neonates are transferred to specialist units for management of congenital disorders; specific protocols for management are available.

Obstetric patients

Scheduled airlines restrict the carriage of pregnant women to those under 32–36 weeks of pregnancy, depending on the airline and the distance to be travelled. Obstetric patients may require an air ambulance transfer for standard medical or surgical reasons. Obstetric indications for air ambulance transfer are: complicated pregnancies in countries with poor healthcare facilities; and premature labour at gestation ages where neonates would be expected to survive if the neonatal facilities were adequate. Transfers may be done before or after delivery.

These are complicated transfers involving two patients, incubator, neonatal staff and staff to care for the mother. If the mother is undelivered, precautions in these cases include supplementary oxygen at altitude, left lateral tilt to prevent aortocaval compression and antacid therapy. There is also the increased risk of thromboembolic events at all stages and prophylaxis should be given unless contraindicated.

Psychiatric patients

Psychiatric patients are observed before flight long enough to assess their suitability for transfer. They can be categorised as patients who are cooperative and can travel as seated passengers, those who are not grossly disturbed but may react badly to travel, and those who are frankly disturbed. Patients in the last two groups may require sedation and adequate monitoring. They may even need to be moved as a stretcher cases, with heavy sedation and the additional escort of a registered psychiatric nurse.

Other problems

Despite the environmental challenges faced by the patient during transfer, the majority of problems arise due to logistic reasons rather a deterioration in the patient's condition, provided that the patient has been adequately assessed and prepared for the journey. In an unpublished audit of air ambulance transfers the most common problems encountered were untoward, and causes included:

- human error
- equipment failure, power failure
- delay in ambulance or aircraft
- problem with medical liaison and transfer of care of patient to transporting team
- customs clearance for drugs and equipment
- injury to medical staff, particularly in loading and unloading
- aircraft problems, such as oil leaks, cabin decompression and other mechanical failures, some requiring emergency landing.

Equipment

All equipment taken should be robust, lightweight and battery powered. The minimal monitoring required for a ventilated critically ill patient is electrocardiogram (ECG), pulse oximetry, blood pressure and end-tidal carbon dioxide. All alarms should be visual and auditory. Two mechanical ventilators should be carried, together with a self-inflating bag for manual ventilation. The ventilators should have adjustable inspired oxygen concentration, variable tidal volumes and frequency. There should be a disconnection alarm, the ability to supply PEEP and to alter the inspiratory/expiratory ratio. The amount of oxygen carried should cover ventilation with an inspired oxygen concentration of 100% for the duration of the journey and with 1–2 h spare. In most countries, transporting road ambulances will carry oxygen.

Equipment and drugs need to be regularly checked and labelled ready for use. They should be comprehensive and packed in easy-access bags (Figure 21.3). For the average air ambulance a total of 12 bags or items are taken, together with 3–4 oxygen cylinders and the personal kit of the medical staff (Table 21.5).

Aircraft

The ideal aircraft should have good access, fitted medical equipment, methods for loading and unloading, be

Figure 21.3 Medical kit for air ambulance transfer.

Table 21.5 Equipment and drugs taken on air ambulance

Defibrillator
Portable suction
Monitor (Propaq)
Two ventilators
Bedding/vacuum mattress/scoop
Oxygen cylinders
Infusion pumps
Battery

Respiratory bag
Intubation pack – kit for intubation
Laedal bag, mask, reservoir
Guedel airways
Oxygen pack – masks, nebulisers, tubing
Intercostal drain set
Ipratropium bromide
Salbutamol
Diazepam
Etomidate
Midazolam
Propofol
Thiopental
Suxamethonium
Vecuronium
Magnesium sulphate
Midazolam
Noradrenaline (norepinephrine)
Propofol
Vecuronium

Others
Aminophylline
Doxapram
Buscopan
Chlorphenamine (chlorpheniramine)
Dexamethasone
Hydrocortisone
Haloperidol
Naloxone
Phenytoin

Minijets
Adrenaline (epinephrine)
Atropine
Calcium chloride
Lidocaine (lignocaine)
Sodium bicarbonate
5% Glucose

Cardiac drugs
Adenosine
Atropine
Digoxin
Hydralazine
Labetolol

Oral
Aspirin
Co-dydramol
Diazepam
Furosemide (frusemide)
Metoclopramide
Nifedipine
Paracetamol
GTN spray/patch
Volterol

Invasive monitoring bag
Heparinised saline 1 litre
Pressure transducers and cables
CVP line, drum catheter, A-lines

Miscellaneous
Variety of syringes, needles, swabs, gloves
Portable blood gas analyser
BNF
Sharps bin
Nurse's bag
Stethoscope
BM stix

Drug bag

Intravenous
Adrenaline (epinephrine)
Amiodarone
Dobutamine
Dopamine
Furosemide (frusemide)
Glyceryl trinitrate
Isoprenaline

Fluids bag
Elohaes 1 litre
Saline 1 litre
5% Glucose 1 litre
Dextrose saline 1 litre
Mannitol p.r.n.
Blood p.r.n.

Figure 21.4 Example of an aircraft used for air ambulance transfer.

comfortable, and have reasonable speed and range (Figure 21.4). The type of aircraft used depends on availability, distance to travel and cost. Aircraft vary from twin prop Beechcraft King Air to small business jets such as the Lear 35 and HS125. In the UK, most operators charter aircraft that are normally used for business purposes. They have little fitted medical equipment other than a stretcher, oxygen supply, suction and drip stand. Some air ambulance companies, particularly the European operators, have their own designated aircraft with fitted medical equipment, while others just have a fitted stretcher, with all other medical equipment carried as separate items. The Civil Aviation Authority (CAA) defines a dedicated air ambulance aircraft as one in which medical equipment has been installed permanently and has been approved by their inspectors. Other non-installed equipment and supplies carried should comply with regulations and be securely stored during flight. The flight commander is in overall charge of the stowage and the decision to use medical equipment.

Stages of a standard air ambulance transfer

Initial information

Once contact has been established between the patient and assistance company, regular updates on the patient's condition are made. A decision is made on the optimal time for transfer and the air ambulance company contacted.

Information received by the air ambulance company on the patient's condition varies widely in content and accuracy, depending on the referring hospital and number of parties involved in the communication chain. Standard information requested is the history of the presenting illness, past medical history, progress of disease and results of investigations or tests. Often very little is received other than a diagnosis and statement that the patient is felt to be fit for transfer. In this situation the air ambulance team must assume the worst case scenario and prepare for all eventualities. The most important information the retrieval team require is whether the patient is cardiovascularly stable, on inotropes, what the ventilator parameters are and what the patient's gas exchange is like. With this information it is usually possible to establish with some accuracy whether it is safe to transfer the patient. It is useful to have a form that can be faxed to the referring hospital requesting this information (Figure 21.5). This should be simple and easy to understand, using internationally recognised terms and translated to the relevant language.

Planning prior to repatriation

This involves planning the transfer, briefing crew, checking equipment and organising aircraft. The duration of ground transfer and flight time should be estimated. Any extra drugs,

PRINCIPLES AND PARCTICE OF TRAVEL MEDICINE

Name…… DoB……

Sex M/F Weight…… Height……

Diagnosis……

Past medical history……

Allergies…… Temp……

Cardiovascular:

HR/Rhythm…… BP…… CVP……Inotropes Y/N

Respiratory:

FiO_2…… Sats…… PaO_2…… $PaCO_2$……BE……

Mode of ventilation…… PEEP…… I:E……

Tidal volume (Vt)…… Rate (f)…… PAP……

Vascular access:

Peripheral line Y/N CVP Y/N Arterial line Y/N

Renal/GIT/Neuro:

Urinary catheter Y/N Urine output……

Nasogastric tube Y/N Diarrhoea Y/N Abdo surgery Y/N

GCS…… Focal signs Y/N Cervical spine stable Y/N

Results: **Drugs and infusions:**

Na…… Hb…… ……

K…… WBC…… ……

Urea…… Platelets…… ……

Creat……Glucose……Clotting…… ……

Figure 21.5 Information request form.

equipment, fluids or blood products not normally carried should be ordered.

Arrival at hospital

It is important to establish a rapport with the referring medical team caring for the patient. They must be given adequate time to hand over the patient, and undue criticism should not be made of any perceived deficiencies in treatment. Once care of the patient has been transferred to the transporting team a full examination and assessment of bedside results can be made. It is now time to make the final decision on whether the patient is fit for transfer. The patient's relatives need to be located and be given a summary of the patient's condition and an explanation of the proposed plan for transfer and the associated risks.

Table 21.6 Checklist for pre-transfer assessment

Before transfer
Staff prepared – fully briefed
ICU bed available
Drugs and equipment checked
Any extra equipment needed

Patient safe to transfer
Respiratory
Airway secure, is intubation required?
Ventilation adequate Pa_{O_2} > 13 kPa
Spo_2 > 95%
Pa_{CO_2} > 4–5 kPa
Chest drain needed?
Cardiovascular
Heart rate/blood pressure controlled and stable
Circulating volume adequate
Intravenous access established and secure
Inotrope infusions moderate and stable
Renal
Catheterised
Adequate urine output
Neurological
Glasgow coma scale stable
No air in skull
Spine stabilised
Abdominal
Nasogastric tube free drainage
Major intra-abdominal haemorrhage excluded
Any further investigations or treatment required?
Established and stable on monitors and transport ventilator

Preparing the patient for transfer

The patient should be optimised for transfer (Table 21.6). The following areas are assessed:

- cardiac output
- oxygenation
- ventilation
- volume status
- intravenous access
- analgesia/sedation
- monitoring
- gas-filled spaces
- thromboembolic prophylaxis.

In patients who are unstable and require resuscitation and ventilation the following order of optimisation is suggested.

1 Administer oxygen and establish monitoring.
2 Secure intravenous access and infuse intravenous fluids.
3 Insert arterial line under local anaesthesia.

4 Rapid sequence induction, intubation and ventilation.
5 Central access.
6 Inotropes if necessary.
7 Urinary catheter.
8 Review patient, check arterial blood gases, chest X-ray if possible.
9 Transfer if stable.

If invasive procedures are to be performed, this should be explained to the referring medical staff as being necessary for a safe transfer. Cases have been reported of the transferring medical staff being forcibly removed from the patient's side by hospital security staff after having initiated an invasive procedure without clear communication to referring medical staff. It may become necessary to delay the transfer to stabilise and review the patient.

During transfer the patient will be moved four times from various beds, trolleys and stretchers. To simplify these movements the patient is placed on a vacuum mattress, which is then secured to a scoop stretcher (Figure 21.6). The scoop stretcher can now be used to lift the patient and can also be secured to the ambulance and aircraft stretchers.

Figure 21.6 Vacuum mattress and scoop stretcher.

Ground transfer to aircraft

Ground transport is usually undertaken in a local ambulance. Most are of good standard with trained crew and adequate equipment. Often the ambulance will pick up the medical crew and equipment from the airfield. This allows the medical crew to assess the quality of the ambulance and possibly leave some of the medical kit on the aircraft. They should always check for the availability of a functioning defibrillator, suction and oxygen before leaving their equipment with the aircraft. Sufficient oxygen should be taken for the duration of the journey and a spare method of ventilating the patient should be carried. Most European ambulances do not have the correct connections for UK portable ventilators; therefore if the ambulance oxygen is to be used during transfer the patient must be hand ventilated. Adequate time should be allowed for traffic congestion and customs controls, which can be lengthy in some countries despite the presence of a ventilated patient.

Arrival at the aircraft

Once the ambulance is clear of customs and on the airfield the aircraft is readied for loading. During this period the patient should be kept in the ambulance, accompanied by one of the medical staff at all times. Once the aircraft is prepared for loading the air and ground crew can be briefed on the plans for loading. The assistance of keen but untrained non-English-speaking ground handlers can cause problems, with intravenous lines being pulled out and potential accidental extubations. In most chartered aircraft, manual loading is required and this involves lifting the patient on a scoop stretcher. Considerable difficulty may be encountered with very tall or morbidly obese patients. Some aircraft have specifically designed loading mechanisms, such as ramps and other crane mechanisms. Once loaded, the patient is reassessed. The monitors and ventilator are checked to make sure that no accidental disconnection or changes to settings have occurred. The medical kit must be stowed securely, with certain essential items being easily available.

Take-off and ascent

During take-off the medical staff monitor the patient carefully for signs of any problems associated with acceleration or gas expansion. At altitude the monitors are adjusted and re-zeroed if necessary. Basic care and monitoring should continue and any indicated therapy instituted. Light aircraft

experience greater effects from turbulence and care should be taken that equipment is secured. In the event of severe turbulence crew should remain seated and use their safety belts.

Descent, landing and second ground transfer

On arrival at the destination airport the medical staff may be fatigued and it is often cold, dark and raining. The ambulance staff should be briefed on the patient's condition and the unloading technique. Transfer to the receiving hospital is carried out at a normal speed; there is very rarely an indication for a 'blue light' transfer. On arrival at the receiving hospital a full medical handover, including details of the transfer, should be made to both nursing and medical staff.

Guidelines

There are a variety of bodies involved in producing guidelines. The recommended standards for UK fixed-wing transfers were published in the *Journal of the Royal Society of Medicine* [16]. The Intensive Care Society and the Association of Anaesthetists have both produced guidelines for the transfer of critically ill patients within the UK and these should be taken as the gold standard when transferring critically ill patients. The major points are summarised as follows.

- The decision to transfer should be made by consultant medical staff after discussion between appropriate medical staff. Transfer should be initiated for patient benefit.
- Fixed-wing aircraft should be used for distances over 150 miles (240 km).
- Specialised air ambulance providers should be used.
- A minimum of two escorts are required: (1) an experienced medical practitioner with training in intensive care and transport medicine, at least 2 years' experience in anaesthesia, intensive care or other equivalent speciality, and competent in resuscitation, airway support, ventilation and organ support; (2) another experienced assistant, either nurse, operating department assistant or paramedic.

Summary

There are an increasing number of medical repatriations into the UK. The majority of cases are stable patients requiring the minimum of intervention. These usually return on a scheduled flight with a nurse escort. Air ambulance transfers of critically ill patients involve a specialist team of anaesthetists and intensive care-trained nurses with previous experience in flight medicine. Most patients can be safely transferred providing they are adequately prepared, optimised and monitored. However, there are risks to transporting any patient. The decision to transfer should involve careful discussion between all the parties concerned, the ultimate aim being a safe transfer with overall benefit to the patient.

References

1. Morton N *et al.* (1997) *Stabilisation and Transport of the Critically Ill.* Churchill Livingstone, London.
2. Kramer W *et al.* (1996) Evaluation of repatriation parameters: an analysis of patient data of the German Air Rescue. *Aviat Space Environ Med* **67**: 885–889.
3. http://www.shephardmedia.com/news/rotorhub/german-air-ambulance-records-38000-missions-during/ (accessed 24 June 2012).
4. Waddell G (1975) Movement of critically ill patients within hospital. *Br Med J* **2**: 417–419.
5. Gentleman D and Jennett B (1981) Hazards of inter-hospital transfer of comatose head-injured patients. *Lancet* **ii**: 853–855.
6. Bion J *et al.* (1988) Transporting critically ill patients by ambulance: audit by sickness scoring. *Br Med J* **296**: 170.
7. Ernsting J *et al.* (1999) *Aviation Medicine*. Butterworth-Heinemann, Oxford.
8. Venkataraman S and Orr R (1992) Intrahospital transport of critically ill patients. *Crit Care Clin* **8**: 525–531.
9. Armitage J *et al.* (1990) Respiratory problems of air travel in patients with spinal cord injuries. *Br Med J* **300**: 1498–1499.
10. Gong H (1992) Air travel and oxygen therapy in cardiopulmonary patients. *Chest* **101**: 1104–1113.
11. Malagon I *et al.* (1996) Changes in cardiac output during air ambulance repatriation. *Intens Care Med* **22**: 1396–1399.
12. Castillo C and Lyons T (1999) The transoceanic air evacuation of unstable angina patients. *Aviat Space Environ Med* **70**: 103–106.
13. Runcie C *et al.* (1990) Blood pressure measurement during transport. A comparison of direct and oscillotonometric readings in critically ill patients. *Anaesthesia* **45**: 659–665.
14. Cruickshank J *et al.* (1988) Air travel and thrombotic episodes: the economy class syndrome. *Lancet* **ii**: 497–498.
15. Gentleman D *et al.* (1993) Guidelines for resuscitation and transfer of patients with serious head injury. *Br Med J* **307**: 547–552.
16. Bristow A *et al.* (1992) A report: recommended standards for UK fixed wing medical air transport systems and for patient management during transfer by fixed wing aircraft. *J Roy Soc Med* **85**: 767–771.

Chapter 22 Venomous bites and stings

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Introduction

Travel throughout the world is becoming easier every year, with air travel enabling any individual with even limited means to visit almost any region. Thus contact with venomous animals, which has in the past been mainly confined to the inhabitants of tropical or subtropical zones, is rapidly becoming a danger worthy of consideration by the world traveller. The traveller should be aware of the hazards of bites and stings by venomous animals and of the safest, simplest and most appropriate methods for dealing with accidents.

Venomous creatures produce venom in a gland or in specialised cells, and can deliver it during a bite or sting. All venoms contain a complex mixture of toxins with widely varying biological, pharmacological and autopharmacological properties. Toxic effects depend on both the type and amount of venom injected. Although death can result from venomous bites or stings, more commonly little or no envenoming occurs as a result of bites or stings by a venomous animal because little or no venom is injected.

SNAKE BITES

Venomous snakes

The majority of venomous snakes have fangs at the front of their mouths, which enable them to inject venom. This is produced by two venom glands, one on each side of the head behind the eye. Each gland is surrounded by muscle, which, on contraction, forces the venom out of the lumen of the gland, along the venom duct, which is positioned on either side of the upper jaw, and then down the canal or groove in the fang. Venomous snakes are divided into two major groups: Family Elapidae (including sea snakes with flattened tails) and Family Viperidae (true vipers [Viperinae] and pit vipers [Crotalinae] possessing a thermosensitive (loreal) pit between eye and nostril to detect warm-blooded prey in the dark). There is also a small group of venomous colubrids (back-fanged snakes), which include the boomslang (*Dispholidus typus*) found in southern Africa and the red-neck keel-back snake (*Rhabdophis subminiatus*) in Southeast Asia. Elapids have short, fixed fangs. Vipers have long, erectile fangs and triangular heads (Figure 22.1). Most snakes have diurnal hunting habits.

Viper bites are much more common than elapid bites, except in the Pacific Australasian area where vipers do not naturally occur. Sea snake bites used to be common among fishing folk of Asian and western Pacific coastal areas but, because of recent modernisation of fishing methods, they have become much rarer. In South and Central America, snakes of medical importance include *Bothrops atrox* (the Barba amarilla, which probably causes more deaths in South and Central America than any other snake) and the tropical rattlesnake (*Crotalus durissus*). In Africa, the puff adder (*Bitis arietans*), cobras (mostly *Naja* species) and mambas (*Dendroaspis* species) cause problems, and the carpet or saw-scaled viper (*Echis* species) is responsible for more snakebite deaths than any other genus in the world, particularly in farmers. In parts of Asia, Russell's viper (*Daboia russelli*), the Malayan pit viper (*Calloselasma rhodostoma*), the saw-scaled viper (*Echis carinatus*), the sharp-nosed pit viper (*Deinagkistrodon acutus*), the Mamushi (*Agkistrodon blomhoffi blomhoffi*), the Habu (*Trimeresurus flavoviridis*), cobras (mainly *Naja* species) and kraits (*Bungarus* spp) are important. Australasia has some of the most venomous land snakes in the world, of which one of the most important species is probably the Papuan taipan (*Oxyuranus scutellatus canni*), a major cause of snakebite death in New Guinea.

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Figure 22.1 Long erectile fangs of a viperine snake.

Epidemiology

Snake bite is mainly a rural and occupational hazard, with farmers, plantation workers, herdsmen and hunter gatherers at greatest risk. Children are frequently bitten due to their inquisitive nature and travellers are also at increasing risk. Most bites occur in the daytime and involve the foot, toe or lower leg as a result of accidentally disturbing a snake; however, some species (e.g. kraits) may bite sleeping victims at night. Bites by sea snakes, although rare, may occur in holiday-makers who swim in the sea or in rivers.

Snake bite statistics based on hospital figures are misleading, because in the rural tropics, where snake bite is common, victims rarely go to hospital, preferring treatment from traditional healers. In Bangladesh, for example, snake bite victims will visit the ohzas, in Sri Lanka the ayurvedic healers and in Ecuador the local shamans. The main problem when patients visit such healers is that the admission of patients to the hospital is delayed and this can result in a fatal outcome.

Enzyme immunossay (EIA) has been used, combined with information from survey questionnaires, to reliably identify specific venom antibodies in the blood of individuals previously envenomed by snakes [1, 2]. Such detailed rural survey procedures reinforce the fact that hospital figures grossly underestimate the real extent of the problem. In the West African savanna, it is estimated that snake bite causes many thousands of deaths per annum, mainly due to the carpet viper, *Echis ocellatus* [3]. Likewise, in Amazonian South America, the incidence and mortality due to snake bite in the indigenous Indian populations is simply not recorded. It is estimated that almost 5% of Waorani Indians in north-eastern Ecuador die annually from snake bite [4]. These risks also apply to travellers, especially in remote areas such as this which are now readily accessible by small aeroplane or by road.

The incidence of snake bite in Sri Lanka, a popular holiday location, is currently one of the highest in the world, with 400 bites and six deaths per 100,000 population per year. Here the most important species medically is Russell's viper (*D. russelii*), which is common in the paddy fields during rice sowing and harvesting [5]. A similar problem exists in Burma where bites by Russell's viper are reckoned to be the fifth most common cause of death. In areas of Thailand, bites by the Thai cobra (*N. kaouthia*) represent a major problem in many rice-growing and fish-farming regions [6]. Further south, in the rubber plantations of Thailand and Malaysia, bites by the Malayan pit viper (*Calloselasma rhodostoma*) are a major cause of morbidity with some associated mortality [7].

Reliable observations suggest that more than half of those sustaining bites escape with minor or no poisoning because little or no venom is injected. However, mortality can be high when adequate medical treatment is not given for serious envenoming, reaching 50% following envenoming by sea snakes (which occurs in 20% of all sea snake bites) and 10–15% in cases of *E. ocellatus* envenoming in West Africa. Snake bite in its early stages is very unpredictable and all victims should be observed closely for at least 24 hours to assess the severity of poisoning and to ensure rational treatment.

A recent literature and modelling analysis on the global impact of snake bite estimated that at least 421,000 people are envenomed annually with approximately 20,000 deaths. These figures may even be as high as 1.84 million envenoming with 94,000 deaths [8].

Avoiding snake bite

For the traveller, there are several measures that are invaluable for avoiding snake bite and these should be strictly adhered to (Table 22.1).

Pathophysiology of snake envenoming

Local envenoming

Venoms contain proteases, haemorrhagins, hyaluronidase, cytotoxins and phospholipases. These act to increase vascular permeability, damage vascular endothelium, and destroy

Table 22.1 Precautions that should be taken to avoid snake bites

- Cut the grass short around houses or camp sites
- Wear proper shoes or boots, and ideally long trousers, when walking in the dark or in undergrowth where snakes are known to occur
- Make a noise when walking in areas where snakes are common
- Use a torch when walking at night
- Avoid sleeping on the ground: snakes are attracted to the warmth of the human body
- Take care after heavy rain: flooding may force snakes into the open in a confined area
- Avoid snakes as far as possible. Do not attack or corner a snake
- Do not handle snakes, even if you think that they are non-venomous
- Never put your hand down holes/burrows or behind wood piles without looking
- Pay attention to warnings by members of the local community
- Take care swimming in waters where sea snakes are known to be active

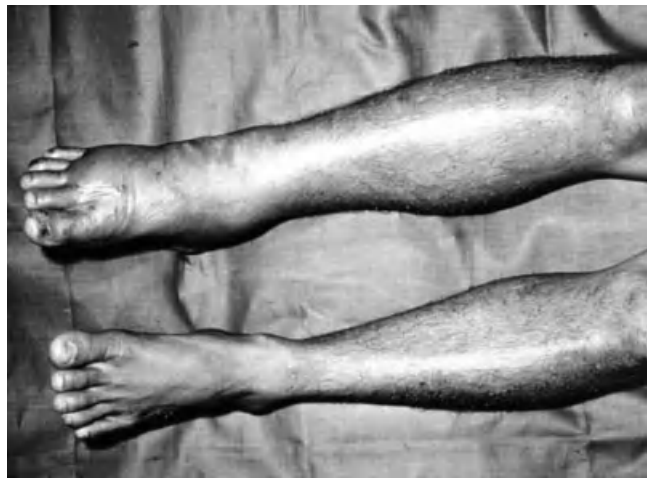

Figure 22.2 Swelling following the bite of a Malayan pit viper. The bite occurred on the dorsum of the right foot.

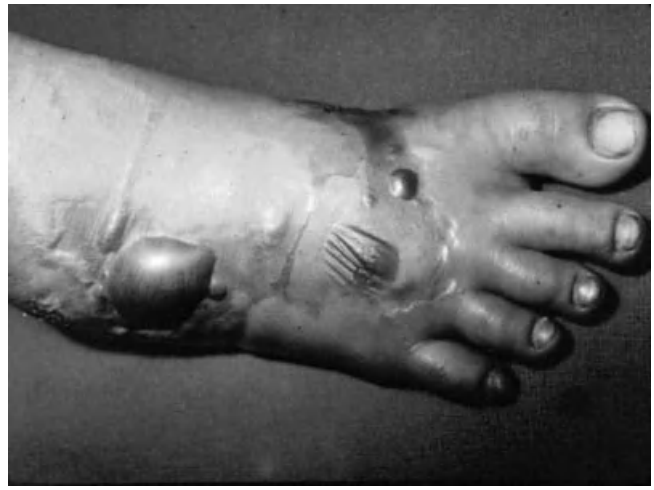

Figure 22.3 Blistering with underlying necrosis after a bite by an Asian common cobra. Similar necrosis occurs in bites by the African spitting cobra, *Naja nigricollis*.

skin and subcutaneous tissue, leading to swelling, bruising and necrosis of a bitten limb.

Early features

Local pain and fang marks are extremely variable and of no help in diagnosis. In bites by some snakes, usually vipers, early blackening at the bite site may be a sign of impending local necrosis or may be due to local bleeding caused by the action of venom haemorrhagins. Local swelling may start within a few minutes of a viper bite if venom is injected (Figure 22.2). It is a valuable clinical sign, because if swelling is absent in a known viper bite, then envenoming may be quickly excluded. Local swelling is also a feature of envenoming in bites by Asian cobras, the African spitting cobra, *N. nigricollis* and certain other African cobras (e.g. *N. katiensis*, *N. mossambica* and *N. pallida*), although it may not appear for 1–2 hours. Bites by other elapids (non-spitting African cobras, mambas, kraits, coral snakes, sea snakes) do not usually cause swelling.

Later features

Local swelling caused by viperine envenoming can extend to the trunk after 2–3 days and may become extensive. Provided necrosis does not develop, it resolves completely in 2–4 weeks, often with discoloration similar to a bruise. Although swelling of a snake-bitten limb may resemble increased intracompartmental pressure in the anterior tibial compartment or the digital pulp spaces, compartmental syndromes are relatively rare and tend to be overdiagnosed in snake bites.

Blisters extending up the limb suggest that local necrosis will follow. This is common in Asian and African spitting cobra bites, and in 5–10% of some viper bites (such as those caused by the African puff adder). Necrosis becomes evident a few days after the bite by a darkening of the skin, together with a 'putrid' smell, which is particularly marked in cobra bite necrosis. Necrosis can be extensive (Figure 22.3) but is

usually superficial; involvement of tendons, muscle and bones is exceptional. Bacterial infection may follow necrosis and may spread to deep tissues. In the absence of necrosis or harmful local 'treatment' measures, such as incisions, fasciotomy or application of dirty dressings, bacterial infection is rare.

Systemic envenoming

Non-specific early signs

There are three important nonspecific early signs of systemic envenoming.

1 Vomiting (sometimes vasovagal but more often denotes systemic envenoming).

2 Hypotension (elapid and viper bites, but not sea snake bites).

3 Regional lymph node tenderness. In envenoming by some species of snake, painful enlargement of the draining local lymph nodes (most commonly in the femoral region) is an extremely useful indication that significant amounts of venom have been absorbed into the lymphatic system.

Specific signs

Specific early signs of systemic envenoming may develop within 15 minutes of the bite but their onset may be delayed up to 18 hours after an elapid bite. Thus, it is important to observe all patients carefully. These specific signs depend on the biting species. Viper bites may result in abnormal bleeding from gums and old wounds, incoagulable blood and shock. In elapid bites the most common feature is neurotoxicity and in sea snake bites there is usually generalised myalgia, myoglobinuria and paresis.

Shock. Hypotension is a prominent feature of envenoming by some species, particularly vipers. Syncope is sometimes reported soon after the bite; this may be an autopharmacological effect due to some venoms containing substances that cause release of endogenous kinins or histamines. Later or prolonged hypotension is usually due to loss of fluid from the circulation because of changes in vascular permeability or because of haemorrhage. Some venoms may also cause direct myocardial toxicity or lead to vasodilatation.

Coagulopathy and haemorrhage. Bleeding may occur from the bite site, injection sites, the gums (Figure 22.4) or old wounds. Blood may be found in the sputum, vomit or stool. Discoid ecchymoses may be observed. Spontaneous capillary haemorrhage may occur into vital organs, especially the brain. The rapid development of intense local haemorrhage and systemic bleeding is a feature of envenoming by a number of species and are due to venom haemorrhagins (potent zinc metalloproteinases) which degrade proteins of the extracellular endothelial matrix and which can also affect platelet function by inhibiting aggregation. In combination with a coagulopathy, they can lead to life-threatening bleeding into tissues such as the brain and the gut.

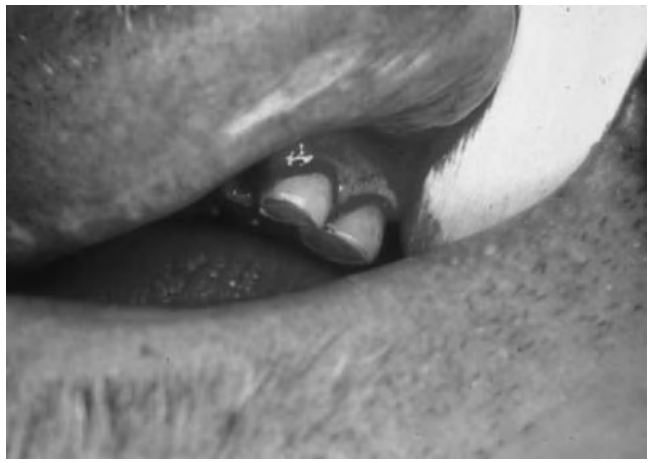

Figure 22.4 Bleeding from the gums following a bite by a Brazilian viper, *Bothrops jararaca* (Reproduced with permission from Professor DA Warrell ©).

The venoms of many vipers and some elapids contain substances capable of activating clotting factors such as prothrombin and/or factors X and V, or converting fibrinogen directly to fibrin. In small animals, the effect of such activities is to cause total intravascular coagulation of the whole circulation, whereas envenomed humans often develop a consumption coagulopathy or a disseminated intravascular coagulation (DIC)-like state, with low fibrinogen levels, prolonged prothrombin and activated partial thromboplastin times, and elevated fibrin(ogen) degradation products. Although some venoms contain substances that act as anticoagulants *in vitro*, these are rarely clinically significant. Thrombocytopenia may occur because of consumption of platelets, but may also be due to a direct effect of venoms on platelet numbers and function.

Neurotoxicity. Ptosis is the most common early sign of neurotoxicity. This may progress to ophthalmoplegia and bulbar paralysis: patients are unable to speak, cough, swallow or protrude their tongue (Figure 22.5). The inability to swallow saliva is an early indication of bulbar involvement. Paralysis of the limbs occurs and ultimately ventilatory failure may occur due to paralysis of the intercostal muscles and the diaphragm. Respiratory paralysis may be preceded by shallow breathing, rise in pulse, respiration rate and blood pressure, increased sweating, cyanosis, confusion and stupor. Coma, non-reactive dilated pupils, twitchings and convulsions presage death. This is a prominent and life-threatening effect of envenoming by many elapids. A vast number of individual neurotoxins have been described and isolated;

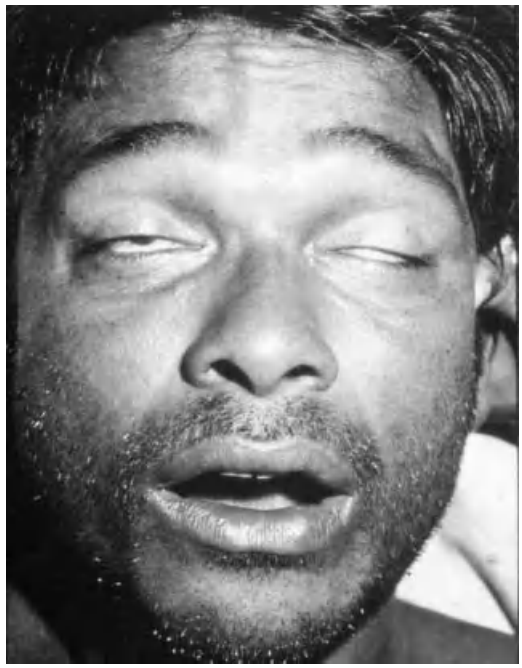

Figure 22.5 Neurotoxic envenoming following a bite by the Indian krait, *Bungarus caeruleus* (Reproduced with permission from Professor DA Warrell ©).

venom from one species often contains a mixture of different neurotoxins. They can be divided broadly by their major site of action: presynaptic or postsynaptic. Presynaptic neurotoxins are predominately phospholipases A_2, which bind with poor reversibility to the motor endplate and damage the nerve terminal, preventing transmitter release. Recovery is by regrowth and resprouting of axons. Postsynaptic neurotoxins bind reversibly to postsynaptic receptors and hence are more amenable to treatment.

Renal failure. There may be oliguria, abnormal electrolytes, and raised urea and creatinine on presentation, but these often develop during the course of envenoming in hospital. Acute tubular necrosis occurs following bites by certain species. In some cases, it may simply be due to the effects of prolonged hypovolemia. However, direct venom nephrotoxicity, DIC, rhabdomyolysis and myoglobinuria are all important mechanisms following bites by some species. Renal ischaemia and renal cortical necrosis may also occur.

Myotoxicity. The venoms of sea snakes, certain rattlesnakes and some Russell's vipers contain phospholipases A_2, which act directly to break down skeletal muscle cells, causing rhabdomyolysis, myoglobinemia and myoglobinuria. Renal failure commonly accompanies this syndrome in untreated patients. Peripheral paresis may occur after some hours, tendon reflexes become depressed then absent. Respiratory failure from muscle weakness may supervene within a few hours or as long as 60 hours after the bite. Some patients succumb from hyperkalaemic cardiac arrest or (later) from acute renal failure.

Cardiotoxicity. Electrocardiogram (ECG) changes have been reported following envenoming by a large number of different species, although clinically significant cardiotoxicity is much less common. These changes are caused by different mechanisms, including a direct effect of venom components on myocardial or conducting tissue function, myocardial damage due to myotoxins or myocardial haemorrhage, or alterations in coronary blood flow due to coronary vasospasm, coronary thrombi or hypotension.

Clinical features

These are summarised in Table 22.2. Fright and anxiety often causes signs and symptoms that may mimic systemic envenoming.

Diagnosis

Severe systemic envenoming is indicated as follows.

- *Vipers.* Shock, swelling extending above elbow or knee, haemorrhagic signs and/or incoagulable blood. T wave inversion and ST depression on ECG.
- *Elapids.* Neurotoxic signs with rapid progression. Shock may also occur. T wave inversion and ST depression on ECG.
- *Sea snakes.* Myoglobinuria and/or signs of respiratory failure. Tall, peaked T waves in chest leads of ECG give warning of impending death due to hyperkalemia or renal failure.

There are exceptions to the rule of haemorrhage and coagulopathy occurring in vipers and neurotoxicity in elapids. Venoms of some Australasian elapids such as the taipan, *O. scutellatus*, cause incoagulable blood and systemic bleeding in addition to causing characteristic neurotoxicity [9]. Venoms of some viperine snakes such as *C. durissus terrificus*, the South American tropical rattlesnake and the South African Berg adder, *Bitis caudalis*, also cause neurotoxic signs. The venom of some viperine snakes (e.g. *C. d. terrificus* and *D. russelii*) may also be myotoxic, causing rhabdomyolysis and myoglobinuria as in sea snake bites.

The diagnostic importance of local swelling in viperine envenoming has already been stressed. For some viper bites, non-clotting blood may be the earliest and only sign of envenoming. This should be looked for by a simple and very sensitive bedside test (WBCT20 [7, 10, 11]) of systemic envenoming (Table 22.3). This test is extremely useful for the diagnosis of systemic envenoming, especially in areas where laboratory facilities do not exist. Along with careful clinical observation, it may also be useful for diagnosing the biting species. For example, in parts of West Africa and Southeast

Table 22.2 Main clinical features of snake bite

Snake	No envenoming (%)	Effects of envenoming		Natural mortality (approximate) (%)	Average death (time)
		Local	Systemic		
Elapids	50	Slow swelling, then necrosis by Asian cobras, African spitting cobras Usually no local effects with other elapids	Neurotoxic effects: Ptosis, bulbar palsy Respiratory paralysis	10	5–20 h
Sea snakes	80	None	Myotoxic effects: Myalgia on moving Paresis Myoglobinuria Hyperkalemia	10	15 h
Vipers	30	Rapid swelling Necrosis in 5–10% (some vipers only)	Haemorrhagic effects and abnormal bleeding Non-clotting blood (some vipers only)Shock	1–15	2 days

Table 22.3 Twenty-minute whole blood clotting test (WBCT20)

- Place a few millilitres of freshly sampled blood in a new, clean, dry glass tube or bottle
- Leave undisturbed for 20 min at ambient temperature
- Tip the vessel once
- If the blood is still liquid (unclotted) and runs out, the patient has hypofibrinogenemia ('incoagulable blood') as a result of venom-induced consumption coagulopathy

Table 22.4 Summary of emergency management procedures for snake bite

- Reassure the patient
- Avoid manoeuvres that may do harm (incision, suction, etc.)
- Immobilise the bitten limb
- Transfer the patient to hospital as rapidly as possible
- A pressure immobilisation bandage may be appropriate if the bite of the snake is unlikely to cause tissue necrosis
- Maintain an airway
- Avoid oral fluids or drugs (especially aspirin or sedatives)
- Take the snake to hospital if it has been killed (care)

Asia, an abnormal clotting test is diagnostic of viper bite and eliminates bites by elapids. Non-clotting blood can also differentiate envenoming by one type of viper from that of another; for example, in Nigeria, *E. ocellatus* envenoming causes non-clotting blood, whereas envenoming by *B. arietans* does not. Recognition of the dangerous local species and their clinical pattern of envenoming is useful in making subsequent treatment decisions.

Definitive diagnosis of the species causing envenoming can only be made if the snake is reliably identified; however, victims seldom bring the snake with them and species identification by the victim or associates at the time of the bite is notoriously unreliable. Although a dead snake is useful, victims or the local population should not attempt to kill the snake as this may result in another bite. Even when the snake is brought to the hospital, medical personnel often misidentify the species.

EIA can provide a more objective, although usually retrospective, means of reliable identification of the species responsible for envenoming [2] by detecting specific venom at the bite site or in body fluids such as serum and urine. Rapid EIA tests have been developed in Australia and may be useful for the traveller in that country. They permit the use of the correct monospecific antivenom for treatment; however, the costs of such tests have precluded their development and use in most developing countries. It is emphasised that the detection of venom on the skin at the bite site does not necessarily mean that envenoming has occurred; other signs of envenoming must be looked for.

First aid and pre-hospital treatment

The aims of first aid for bites and stings by snakes and other venomous animals is to treat or delay life-threatening effects that may develop before the patient reaches medical care, to hasten the safe transfer of the patients to a medical facility and to avoid harmful measures (Table 22.4).

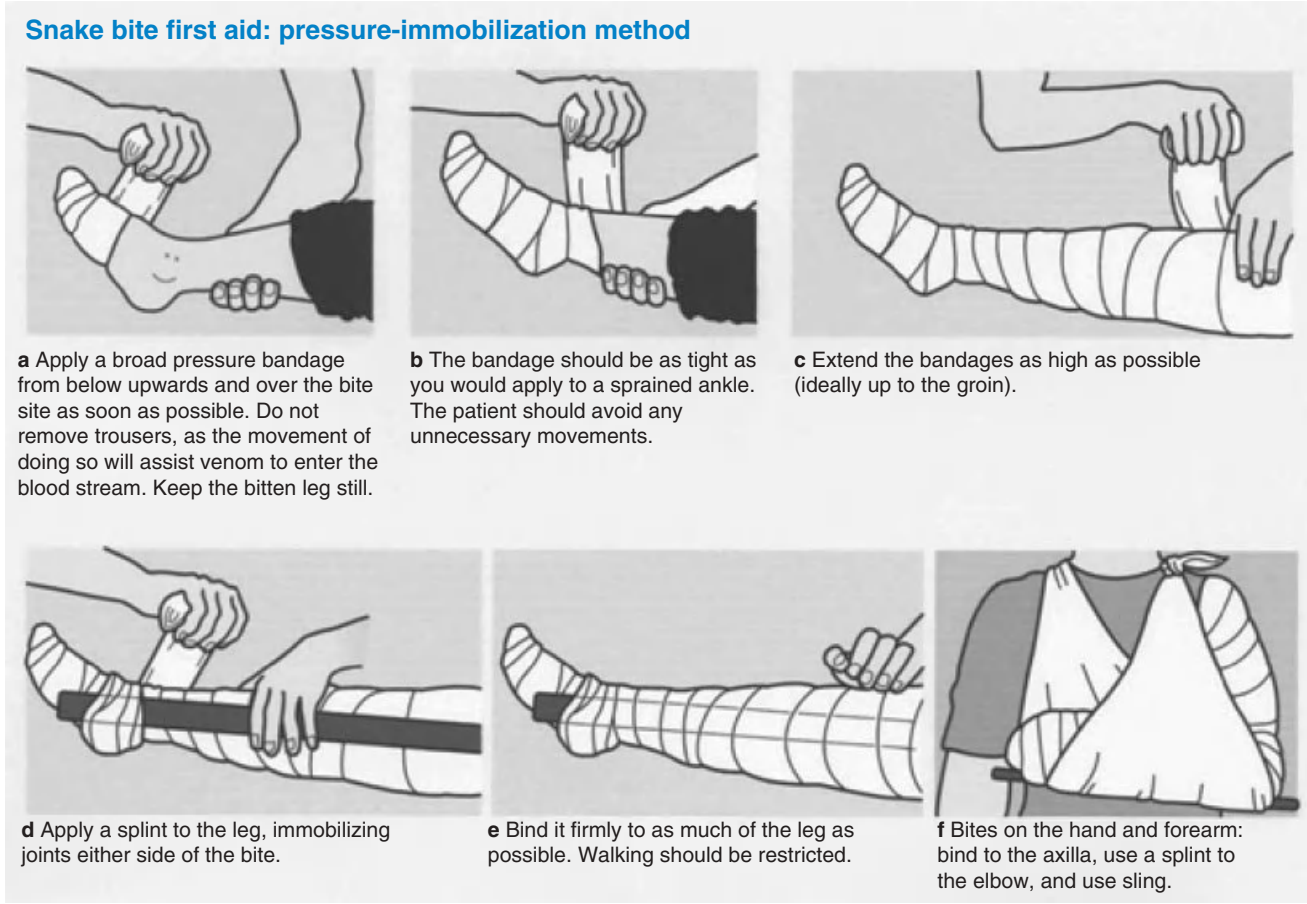

Figure 22.6 Crepe bandage technique for limb immobilisation following snake bite (Reproduced with permission from Professor DA Warrell ©).

1 Panic is a common response to snake bite. The patient should be reassured that not all bites result in envenoming, that most snakes are non-venomous and that modern hospital treatment is effective.

2 Harmful measures should be actively avoided. Wound incision is not beneficial, will aggravate bleeding in victims who have a venom-induced coagulopathy, may damage nerves and tendons, and may introduce infection. Application of suction is ineffective in removing venom from the wound and it may introduce secondary infection and aggravate the problems of local necrosis. Tourniquets or constriction bands should be avoided. Electric shock therapy, application or injection of chemicals locally to the site of the injury, local application of ice packs, and excessive and potentially dangerous traditional methods (e.g. black snake stone, forcible inhalation of oil) should be avoided.

3 The patient should be rapidly transferred to the nearest medical centre. Minimising movement of the bitten limb by splinting will delay the spread of venom from the bite site through the lymphatic system into the circulation.

4 If evacuation time to a hospital or clinic with antivenom facilities is likely to exceed 30 minutes, a pressure bandage may be applied to delay absorption of venom via the lymphatics. A compressive crepe bandage should be applied firmly, as for a sprain, over the bite and up the entire limb [12] (Figure 22.6). The limb should then be immobilised. This bandage, or alternative, should not be released during transit. This procedure is most appropriate for bites by snakes whose venom does not cause local necrosis and swelling (e.g. Australasian elapids, kraits, coral snakes, sea snakes). If there is uncertainty about the biting species, it may be used but has the potential to worsen the local cytolytic effect if used for snakes with necrosis-inducing venoms by concentrating the venom at the bite site.

5 Food, alcohol, drugs (especially aspirin or sedatives) or drinks should be avoided unless necessary to avoid dehydration.

6 A clear airway should be maintained by lying the patient head-down on the side. This will prevent aspiration of vomit or oral secretions. If a patient stops breathing, expired air

Table 22.5 Initial clinical assessment of the envenomed patient

- Whole blood clotting test (WBCT20). This should be repeated at 6-hourly intervals if envenoming by a viper whose venom causes fibrinogen consumption is suspected
- Careful examination of gums, injection sites and old wounds for signs of bleeding
- Examination for ptosis, limb weakness or difficulties in breathing, talking or swallowing
- Regular recording of pulse, respiration, blood pressure and urine output
- Examination for muscle tenderness and myoglobinuria in sea snake bites
- Measurement of limb swelling (comparing the circumference at different levels with unbitten limb)
- Recording of local necrosis (skin colour, blisters, putrid smell)
- Electrocardiograph

Table 22.6 Useful laboratory tests in envenoming

White blood cell count
Hemoglobin level
Platelet count
Prothrombin time, APTT and fibrinogen levels if available
Serum urea and creatinine
Creatine phosphokinase (CPK) (reflecting skeletal muscle damage)

ventilation with or without external cardiac massage should be commenced. In patients with severe neurotoxicity, artificial ventilation can be successfully maintained for a number of hours until the patient reaches medical care.

7 If the snake has been killed, it should be taken to the hospital with the victim. Careful handling is necessary: the biting reflexes of a recently dead snake may cause a second bite.

8 Introduction of venom into the eye by the African and Asian spitting cobras should be treated by liberal irrigation with water or other available bland fluids (e.g. milk or even urine).

Early management

Initial assessment

It is very important that staff neither panic nor dismiss a case of snake bite as trivial without proper observation. Except for cases in which envenoming can be reliably excluded, the patient should be carefully observed for at least 24 hours; fatalities have occurred in patients discharged from hospital with presumed minor envenoming only. Initial observations that should be performed are shown in Table 22.5 and useful laboratory tests in Table 22.6.

Local site

On admission to hospital, once antivenom is available any compression bandage or tourniquet applied earlier should be released. Sudden systemic envenoming can occur following removal of tourniquets; patients should therefore be carefully observed. The site of the bite should be left alone. Local dressings should not be applied as they increase the risk of secondary bacterial infection. Blisters should be aspirated using a sterile syringe as they may contain large amounts of free venom which could theoretically gain later entry to the circulation and exacerbate the clinical situation.

Although bacteria are found commonly in the oral cavities of snakes [13], infection at the site of the wound is relatively uncommon unless skin necrosis is present. Routine antibiotic prophylaxis is therefore not recommended unless necrosis is present. The commonest organisms found from infected clinical specimens are Gram-negative, but Gram-positive aerobic cocci and anaerobes also cause problems. From the few limited clinical studies, chloramphenicol or a combination of penicillin and an aminoglycoside would be suitable initial therapy until sensitivities become available. Tetanus toxoid should be given to all patients.

Antivenoms

Indications for use

Antivenom can reverse systemic effects of the venom when given hours or even days after the bite. The major indication for its use is systemic envenoming (usually neurotoxicity, incoagulable blood and bleeding or hypotension and shock). Antivenom should not be given routinely in all cases of snake bite because of adverse anaphylactic-type reactions in about 1–80% [14] of individuals, depending on the antivenom. It is also expensive, often in short supply and should therefore not be used unnecessarily [15, 16].

The indications for the use of antivenom in local envenoming are less clear. However, antivenom treatment should be considered in patients presenting within hours of a bite who have swelling extending to cover more than half the length of the bitten limb.

Choice of antivenom

Antivenoms are produced by immunising large animals (usually horses) with gradually increasing amounts of

venom. Once hyperimmunised, the animal is bled and the plasma or serum harvested. Pools of individual venoms obtained from a large number of snakes of the same species are used; this eliminates venom variation, which can be extensive even within single species from the same geographical area. If a venom pool from a single species is used for immunisation, the serum is termed monospecific; if venom from more than one species is used, it is termed polyspecific. Monospecific antivenoms are theoretically more effective and less likely to cause reactions than polyspecific antivenoms as less foreign protein is required for treatment. They are useful when the snake can be definitively identified or when there is one predominant venomous species in a particular area. Polyspecific antivenoms are useful when the species of the biting species is not known and usually will cover most of the important venomous species within a particular area.

Although whole purified or crude IgG has been used in the past, most commercial antivenoms currently produced use pepsin to remove the Fc fragment, leaving an antivenom composed of $F(ab')_2$ fragments (Figure 22.7). Providing that the Fc fragment has been effectively removed during the purification procedure, $F(ab')_2$ antivenoms do not bind complement or macrophages, eliminating a common source of antivenom reactions. Smaller Fab fragments prepared from the whole IgG molecule by papain digestion [17] have theoretical advantages as they do not form immune complexes of sufficient size to cause type III hypersensitivity

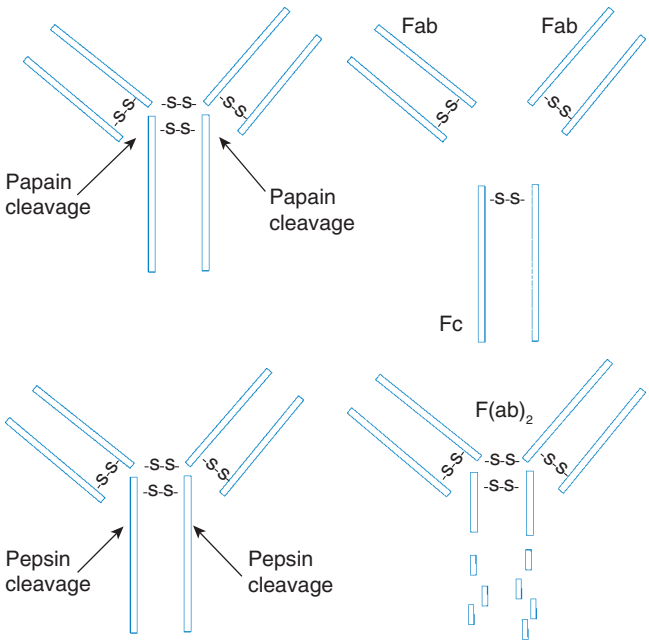

Figure 22.7 Schematic representation of the IgG molecule highlighting both $F(ab')_2$, Fab and Fc regions.

reactions, have greater volumes of distribution and more rapid kinetics than either IgG or $F(ab')_2$ [18] and may penetrate tissue spaces better. However, Fab is more rapidly cleared from the circulation via the kidney than $F(ab')_2$, which can necessitate the administration of further doses; the disadvantages of a Fab antivenom probably outweigh the potential advantages. Recently, caprylic acid-purified IgG has been shown to constitute highly effective and cheap antivenoms with a relatively low early reaction rate [19–21]).

Dose and administration

The dose of antivenom is primarily dependent on its neutralising efficacy and varies considerably between different products; local advice should be sought as manufacturer's instructions are often incorrect. The recommended initial doses of antivenom may depend on the severity of envenoming. Doses of antivenom for children are the same as those for adults because the amount of venom introduced by the snake bears no relationship to the age or size of the victim.

Ideally, antivenom should be diluted in saline and be given by intravenous infusion. The infusion should be started slowly and the rate progressively increased so that it is completed within 1 hour. In the absence of infusion apparatus, antivenom can be given by slow direct push injection over 10–15 minutes. Before use, antivenom should be checked for any opacities, which precede loss of potency. Clear antivenom is fully effective and, in areas where it is in short supply, expired antivenom that retains its clarity should not be discarded.

The administration of further doses of antivenom is dependent on careful observation of the patient's clinical response to antivenom. Correction of a venom-induced coagulopathy is a good marker of the efficacy of antivenom in patients envenomed by viperine snakes. On admission to hospital such patients often have incoagulable blood. Six hours after antivenom, the WBCT20 should be repeated [10]. If the blood is still non-clotting, then a further dose of antivenom is indicated. As incoagulable blood can reoccur after apparent successful treatment with antivenom, the WBCT20 should be repeated at 6-hourly intervals for the first 2 days. Recent studies have challenged the utility of antivenom for treating coagulopathy in Australasian elapid envenoming, but further research is needed [22].

It is more difficult to judge the need for further antivenom when the predominant problem is neurotoxicity. If postsynaptically induced neurotoxic signs fail to resolve rapidly, then further doses of antivenom should be given; however, for presynaptically binding neurotoxins, signs are more difficult to reverse.

EIA can be used as a research tool to look at the rate of permanent venom clearance and may help to determine the

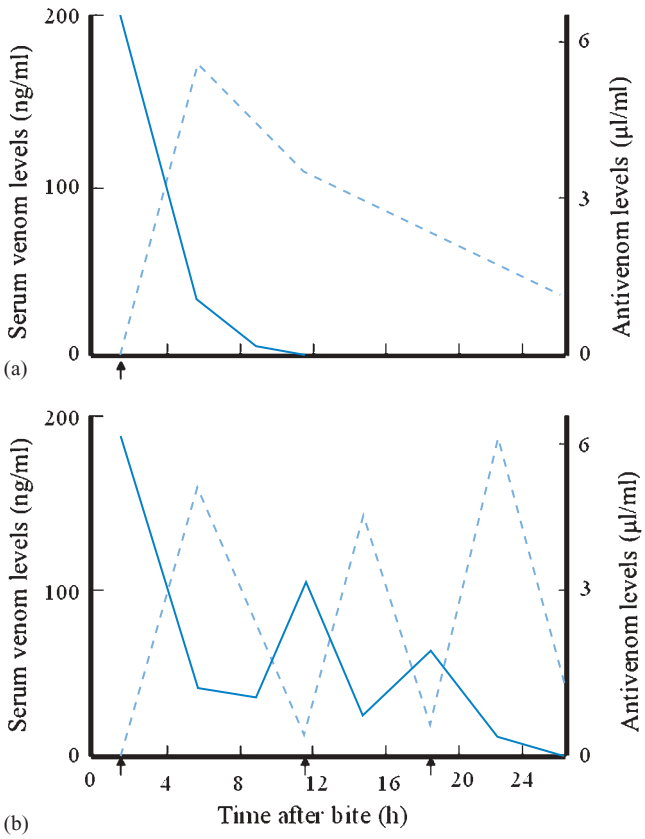

Figure 22.8 Venom and antivenom levels in a patient treated with: (a) an effective antivenom and (b) a relatively ineffective antivenom. Venom levels are shown by unbroken lines and antivenom levels by broken lines. Arrows indicate the time when antivenom was administered.

optimum dose of a particular antivenom (Figure 22.8). The time taken by the antivenom to clear venom permanently from the circulation correlates well with correction of venom-induced systemic effects, such as the restoration of blood coagulability.

Antivenom reactions

Early reactions

Most early antivenom reactions are due to complement activation caused by $F(ab')_2$ or Fab aggregates in the antivenom. The incidence of antivenom reactions is closely related to the quality of purification of antivenoms; the use of caprylic acid-purified IgG may reduce antivenom reactivity as there are no aggregates [19–21]). Both immediate (potentially life-threatening) and delayed serum reactions are more common with polyspecific than with monospecific antivenoms because of the larger volumes of antivenom required. Although intravenous infusion is advocated, there are no significant differences in the incidence of early reactions when antivenom is administered by slow intravenous push injection or by slow intravenous infusion [23].

All patients given antivenom treatment should be regarded as likely to have a reaction, although the incidence of reaction varies widely between different antivenoms (1–80%) [14]. Adrenaline (epinephrine) should be drawn up for use before the infusion is started. The initial drip rate should be slow and at the first sign of any anaphylactoid reaction (e.g. a few spots of urticaria, start of itching, tachycardia or restlessness) antivenom infusion should be temporarily stopped. Adrenaline (0.5 mg; 0.5 ml of 1:1,000 adrenaline) should be injected intramuscularly into the deltoid muscle. In the case of children, the recommended dose is 0.01 mg/kg body weight intramuscularly. This is usually quickly effective. The antivenom infusion can then be cautiously restarted, along with antihistamine treatment.

Skin sensitivity tests have no predictive value for reactions [24] and should not be used. A history of a significant allergic reaction to antivenom is a relative contraindication to its use unless the risk of death from envenoming is high. In that rare event, small amounts of adrenaline, (0.2–0.5 ml of 1:1,000 adrenaline solution) should be given subcutaneously before antivenom administration and should be repeated if a reaction occurs.

Routine prophylaxis has been controversial. Adrenaline, antihistamines and steroids have all been used around the world with small trials suggesting that adrenaline prophylaxis reduced the incidence of early antivenom reactions [25]. A recent large study demonstrated that routine adrenaline prophylaxis reduced the risk of severe antivenom reactions but that hydrocortisone and promethazine were not effective [26]. Routine adrenaline prophylaxis should be considered in settings where close observation of patients is not possible during antivenom administration.

Pyrogenic reactions

Some antivenoms contain impurities (endotoxins) due to inadequate purification and can cause pyrogenic reactions. These are treated by cooling the patient physically, giving antipyretics such as paracetamol by mouth, and intravenous fluids to correct hypovolemia.

Late serum sickness reactions

These usually occur 7–10 days after antivenom and are treated with an oral antihistamine combined with a steroid such as prednisolone (15–20 mg/day).

The traveller and antivenom

In general, it is not recommended that the overseas traveller carries antivenom when visiting areas in which snake bite is a problem for the following reasons.

1 Hospitals in areas where bites are a problem would normally be expected to stock appropriate antivenoms.

2 Antivenom can cause severe and potentially life-threatening reactions and must therefore be administered in a hospital environment (preferably under intensive care conditions).

3 It must be given by the intravenous route requiring qualified personnel.

4 It is a waste of time to give antivenom locally or by any other route.

5 Antivenoms should be stored at 4°C.

However, where antivenom is unavailable locally, purchasing it in advance after taking expert advice is recommended (http://www.toxinfo.org/antivenoms and http://apps.who.int/bloodproducts/snakeantivenoms/database/). Ideally, polyspecific antivenom would be the most appropriate. In the event of a bite, the antivenom should be taken to the hospital with the victim. In most circumstances, even in remote areas when incidents happen, arrangements can be made to get the bitten individual rapidly to hospital.

Supportive therapy

Although antivenom is of prime importance in treating snake bite, supportive therapy of the patient may be crucial in minimising both mortality and morbidity. This includes protecting the airway, possibly by assisted ventilation in the case of neurotoxic envenoming and the use of anticholinesterase drugs (evaluated by 'Tensilon testing'). These drugs are not effective for venoms that cause presynaptic neuromuscular blockade.

Strenuous efforts should be made to prevent complications from bleeding in a patient with coagulopathy. Intramuscular injections and invasive procedures should be avoided. After treatment with antivenom, the restoration of normal clotting is dependent on the hepatic synthesis of clotting factors, which takes several hours. There is no role for clotting factors, fresh frozen plasma or fresh blood until sufficient antivenom has been given to neutralise venom procoagulant components. Fluid replacement or blood transfusion may occasionally be indicated in viperine shock, but specific antivenom is usually dramatically successful if given in adequate dosage.

In the event of renal impairment, careful fluid balance is required. Peritoneal dialysis can be set up in quite primitive conditions and has been used very effectively. Renal impairment in association with rhabdomyolysis and myoglobinuria (as in sea snake bites) may be avoided by the early use of alkaline diuresis and mannitol.

As soon as local necrosis is obvious, sloughs should be excised. There have been good results with the use of early skin grafting, even if infection is still evident. As previously discussed, the considerable swelling following bites by some species may lead to clinical suspicion of compartmental syndromes. Fasciotomy should not be considered unless the intracompartmental pressure exceeds 45 mmHg (less in children). Special care may be needed with the management of bites affecting the pulp space of the fingers. It is vital that haemostatic disorders are corrected before surgery; many patients have bled to death from unnecessary fasciotomies.

Some cobra species in Africa and Asia are able to 'spit' up to 2 metres from fang tips whose venom duct exits are directed forwards instead of downwards. Affected eyes should be thoroughly irrigated with liberal amounts of water. If the eyes are promptly bathed with water, only mild inflammation results. Instillation of 0.5% adrenaline drops is reported to relieve the pain and inflammation. Because of the slight risk of corneal abrasion, examination by fluorescein staining or slit lamp is advisable. Otherwise, topical antimicrobials such as tetracycline or chloramphenicol should be applied.

If antivenom is not available

In many areas of the world, appropriate antivenoms are sometimes unavailable. If neurotoxicity occurs, supportive therapy as indicated above (airway management and artificial ventilation) can prevent death. Recovery from neurotoxicity will eventually occur, although this may take a number of days. Coagulopathies may also recover spontaneously; avoidance of trauma and prevention of bleeding become the major priorities. Fresh frozen plasma, clotting factors, cryoprecipitates or fresh whole blood can be transfused to prevent serious or life-threatening bleeding, providing the coagulopathy has resolved.

SCORPION STINGS

Scorpions have four pairs of legs, a pair of claws, a body with a broader front part and a six-jointed, tail-like abdomen. The terminal segment of the 'tail' is called the telson (Figure 22.9) and contains two venom glands connecting with the curved, needle-sharp sting, which is used either in defence or in obtaining food. The tail with its sting is always brought forward in front of the scorpion.

In many areas of the world, scorpion stings are medically more important than snake bites. Such areas include Mexico,

Figure 22.9 Scorpion, with young, showing the terminal segment or telson, which contains two venom glands. The sting is always brought forward over the abdomen.

Trinidad, parts of Brazil, North Africa, the Middle East and India. In Mexico there are about 300,000 cases a year, with about 1,000 deaths [27]. The problem in some areas is also increasing; for example, in Minas Gerais State in Brazil, *Tityus serrulatus* is rapidly colonising urban areas. During the day, scorpions hide under stones, in cracks, among debris or in clothing; desert species often burrow, sometimes to a depth of 2.5 m. The five genera most dangerous to humans are *Centruroides* (southern United States, Central America), *Tityus* (South America), *Androctonus* (Africa), *Leiurus* (Africa and Middle East) and *Buthus* (Africa, Middle East, Asia).

Avoiding scorpion sting

The traveller in areas where scorpions are common can take certain simple precautions. Shoes should be worn when walking in the dark, clothes, socks and footwear should be checked carefully for scorpions by shaking them in the morning before dressing, a torch should be used when searching in dark areas such as cupboards, storing domestic rubbish near the house should be avoided and travellers, especially children, should be actively discouraged from handling scorpions.

Clinical features

These are partly dependent on the amount of venom injected relative to the weight of the victim. Pain around the bite site is the commonest feature; this can be severe and last from several hours to 1–2 days. Local erythema and swelling are unusual, but itching and paresthaesia may be prominent and last for many days. Systemic envenoming is rare but more common in children than adults, occurring within several minutes of the bite in severe cases. Symptoms and signs are caused primarily by activation of the autonomic nervous system by venom components, leading to an 'autonomic storm' (Table 22.7).

Table 22.7 Major signs and symptoms of scorpion envenoming

Tachypnoea
Excessive salivation
Nausea and vomiting
Lacrimation
Sweating
Abdominal pain
Muscle twitches and spasms
Hypertension
Pulmonary oedema
Cardiac arrhythmias
Hypotension
Respiratory failure

In severe envenoming, the cardiovascular manifestations of severe hypertension, acute pulmonary oedema with respiratory failure (due to pulmonary oedema, bronchial hypersecretion and paralysis of respiratory muscles) and myocardial failure are particularly prominent. Both tachycardias and bradycardias are common. Acute pancreatitis has been reported in *Tityus* envenoming and, in India, necropsy evidence of intravascular coagulation has been reported following *Buthus* stings.

Treatment

First aid consists of reassuring the victim, immobilising the limb and reaching hospital rapidly. If local pain is severe, the area should be infiltrated through the puncture wound with 2–5 ml 1% lidocaine (lignocaine) hydrochloride. Alternatively, opiates may be used, but care must be taken not to cause respiratory depression. Local injection of emetine hydrochloride should not be used as it may cause local necrosis. Specific scorpion antivenom is available in many parts of the tropics, although supplies are variable. It is indicated, especially in children, for systemic envenoming (ideally, by intravenous infusion as in snake bite, but intramuscular administration may be effective). When antivenom is not available, supportive treatment is indicated. Prazosin appears to be effective in treating hypertension and cardiac

failure; it may block the action of scorpion venom peripherally. Nifedipine has also been used to manage hypertension; opinion is divided on its efficacy and it should probably only be used in combination with prazosin. Pulmonary oedema should be treated by conventional means; intravenous vasodilators may be needed in severe cases. Subcutaneous atropine and intravenous calcium gluconate have been advocated to alleviate systemic symptoms, but evidence of their efficacy is lacking and they could theoretically be harmful.

SPIDER BITES

As with scorpions and many snakes, the harmfulness of a spider cannot be judged from its appearance; many of the large, fearsome, tarantula-like spiders are harmless to humans. The most dangerous are the black widow spiders of the genus *Latrodectus* (most tropical and subtropical countries including North America, Argentina, the Mediterranean region, Middle East, southern Russia, Arabia, Ethiopia, southern and eastern Africa, Madagascar, south and South-east Asia, and New Zealand) and the brown recluse spiders of the genus *Loxosceles* (American continent, the Mediterranean region and the Middle East). The bodies of these spiders measure only 1 cm in length (Figure 22.10).

In Australia, bites by the funnel-web spider (*Atrax robustus*) are fairly common. The aggressive Brazilian wolf spider, *Phoneutria nigriventer*, is distributed from southern Brazil to Central America and and frequently bites humans, although very few deaths have been recorded. Spider bite may be difficult to diagnose as the spider responsible is often not found. It is usually the female spider that is responsible for envenoming as, being larger than the male, it can inject more venom.

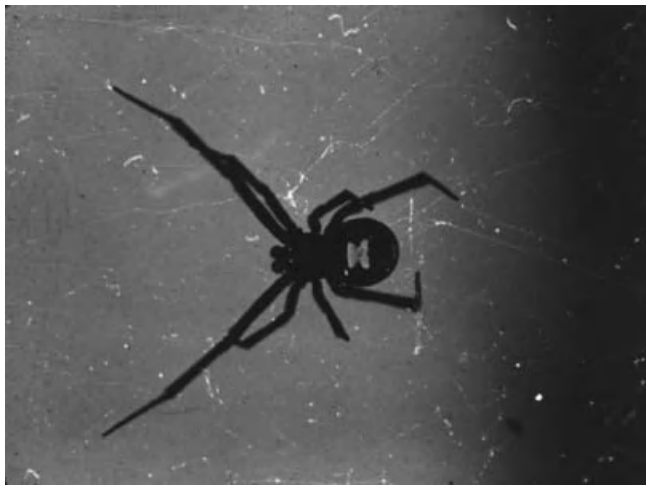

Figure 22.10 The black widow spider, *Latrodectus*, showing the typical abdominal red marking.

Avoiding spider bite

It is difficult to avoid bites because the medically important spiders are usually small. Keeping houses/huts free of insects likely to attract spiders may help. If the spider responsible for the bite is killed, it should be taken to the hospital for identification. All spiders are venomous and many can cause a painful bite; however, fortunately only very few species can cause severe problems.

Clinical features

Latrodectus spp are not usually aggressive and always bite in self-defence. *L. mactans* is the most dangerous species. The predominant symptom is pain at the bite site within 1 hour becoming severe. Bite site reactions are often slight or, at most, demonstrate slight blanching, erythema or urticaria. The majority of patients do not develop systemic signs or symptoms.

In patients with systemic envenoming, the pain may spread from the site to local lymph nodes and become either generalised or affect parts of the body close to the bitten limb. This may take a number of hours to occur. Abdominal pain is common in lower limb bites, and may mimic an acute abdomen. Other features of systemic envenoming are mainly due to transmitter release from skeletal and autonomic nerve endings (Table 22.8).

Patients may have a flushed and sweating face, swollen eyelids, blepharoconjunctivitis and a painful grimace ('facies lactrodectismica'). Hypertension is also a characteristic

Table 22.8 Symptoms and signs of latrodectism

Sweating
Hypersalivation
Rhinitis and lacrimation
Nausea and vomiting
Intense cramp-like muscle pain
Generalised weakness
Tachycardia or bradycardia
Hypertension
Breathing difficulties
Insomnia and mental agitation
Restlessness and feeling of impending doom
Generalised rash (late)

Figure 22.11 Bite by a spider of the genus Loxosceles showing the black eschar.

feature of systemic lactrodectism and may be severe. Electrocardiographic abnormalities have been observed but deaths are rare. Recovery is usually complete within 24 hours but can take up to a week. Weakness, fatigue, pains, headaches, drowsiness and impotence may persist for several months.

The clinical picture following *Loxosceles* bites is quite different. Although the initial bite may be painless, local pain subsequently develops over a number of hours; patients may present 12–48 hours after the bite. A slowly evolving white ischaemic area surrounded by redness and extravasated blood may be seen at the site of the bite. The white area later turns violaceous, then black and dry by 3–7 days (Figure 22.11). The eschar separates, leaving a deep ulcer which heals slowly within 3 weeks to 5 months, sometimes causing severe scarring. Very rarely, systemic manifestations of haemolysis, haemoglobinuria, DIC and ultimately acute renal failure may occur.

The Sydney funnel-web spider, *Atrax robustus*, is medically the most important species of the genus *Atrax* but, in most bites, systemic envenoming does not occur. However, the large fangs and aggressive attack of this spider may result in intense local pain of short duration. Systemic envenoming may develop rapidly, initially causing numbness around the mouth and spasm of the tongue. Nausea and vomiting, abdominal pain, profuse sweating, and excessive salivation and lacrimation may develop. Muscle fasciculation and spasms occur and changes in mental state leading to coma may be observed. Severe hypertension and arrhythmias may occur in the first few hours and acute pulmonary oedema is particularly problematic in children. In some untreated patients, symptoms appear to settle before progressive hypotension occurs, which may culminate in irreversible cardiac arrest.

Systemic envenoming does not occur in the majority of *Phoneutria* bites. Local burning pains at the site of the bite usually radiate to the entire limb and even to the trunk within 10–20 minutes of the bite. When it occurs, systemic envenoming may develop rapidly, initially causing tachycardia, hypertension, vertigo, fever and sweating (mainly in the neck region). Loss of sight, nausea, vomiting, abdominal pain and priapism, particularly in children, may occur. Confusion, bradycardia, hypotension, pulmonary oedema and shock may occur in severe cases.

Treatment

The pressure immobilisation first aid method is advocated for bites by *Atrax* species, but there are no other specific methods for bites by other species. Antivenoms against spider venoms are produced for treating systemic *Latrodectus* envenoming in Australia, South Africa and Croatia; antivenoms are produced against *Loxosceles* and *Phoneutria* venoms in Brazil. They should be administered in the same way and using the same precautions as in snake bite.

In *Latrodectus* envenoming, antivenom, if available, is indicated for systemic envenoming and many would advocate its use for any significant symptoms. Many other therapies have been used, either as adjuncts to or instead of antivenom, including intravenous calcium gluconate, muscle relaxants such as diazepam, opiates, atropine and chlorpromazine.

Antivenom is relatively ineffective for bites by *Loxosceles* species because many patients present late after the bite when necrosis is already established. Therapy with dapsone is sometimes used, although there is no proven benefit. Steroids have received both favourable and unfavourable comment, but small trials show no benefit. The role of surgery is also controversial; many surgeons now believe that surgery should not be performed until clear demarcation of the necrotic lesion has occurred, and skin grafting only appears to be necessary in around 3–5% of patients.

Antivenom for funnel-web spider bites has significantly improved the prognosis following bites by this species and is indicated for any patient with systemic envenoming. Intensive care support may be required to control pulmonary oedema and circulatory failure. Although excessive autonomic nerve activity appears to be involved in the pathogenesis of severe envenoming, pharmacological intervention is not usually required.

BEE, WASP AND HORNET STINGS

Until recently, the main medical problem posed by bee and other hymenopteran stings has been the development of

hypersensitivity with the risk of fatal anaphylaxis. However, multiple stings by honey bees and other hymenoptera can cause fatal envenoming; in adults up to 400–600 bee stings and in children 30–60 stings are enough to cause death by direct toxicity, although survival has been reported after as many as 2,243 stings. Following the introduction of the aggressive Africanised honey bee (*Apis mellifera scutellata* or *A. m. adamsonii*) into South America in 1957, mass attacks in humans have become more common. Three out of five victims died after mass attack in São Paulo state, Brazil [28]. It is estimated that there were 700–1,000 such deaths in Latin America between 1957 and 1985.

Clinical features

Local pain is the most common feature; however, victims with multiple stings may develop rhabdomyolysis (myoglobinuria and myoglobinemia), intravascular haemolysis, hepatic dysfunction, hypertension and myocardial damage, possibly due to the release of endogenous catecholamines by venom phospholipase A_2 and mellitin. Patients may develop respiratory distress with acute respiratory distress syndrome (ARDS), shock, coma, acute renal failure and bleeding. Laboratory findings include a severe neutrophil leucocytosis in addition to evidence of rhabdomyolysis and impaired renal and hepatic function.

Another serious, and much more common, aspect of wasp, bee and hornet stings is allergy. If highly sensitised, symptoms may start within a few seconds, with tingling of the scalp, vasodilatation, hypotension and death within 1–2 minutes. In most patients, the reaction begins after 1–2 minutes with generalised urticaria, followed over the next hour by oedema of the glottis, bronchoconstriction, hypotension and coma. Subsequent reactions to further stings start progressively sooner and may be more severe. Delayed allergic reactions may also occur 1–7 days after the sting, with fever, urticaria, enlarged lymph nodes, joint pains and leucocytosis. These episodes usually last between 1 and 2 weeks.

Treatment

The sting, a tiny black shaft with the white poison sac attached to its free end, should be carefully removed. It should not be grasped with forceps or fingers as this can express more venom from the sac into the skin, but should be scraped from the flesh with the fingernail or the blade of a knife. Local antiseptic should be applied and pethidine given for pain if necessary. Meat tenderiser is claimed to relieve all pain in seconds, when rubbed into the skin in a dilute solution (1:4 ratio of tenderiser to water). Papaya extracts in the tenderiser provide papain, which may break down venom and kinins at the site of the sting.

No antivenoms are currently available commercially to treat multiple stings. A prototype antivenom has been produced in Brazil by the Instituto Butantan, which is highly effective in an experimental animal model; clinical trials are currently underway in humans. In a patient with multiple envenoming, the first priority is to remove as many stings as possible, thus limiting the amount of venom injected. Serious complications, such as intravascular haemolysis and the consequences of rhabdomyolysis, should be anticipated. Renal failure may be avoided by the early use of mannitol and bicarbonate. The empirical use of large doses of antihistamines and corticosteroids may be helpful in treating the massive release of histamine; drugs such as prazosin and nifedipine have been advocated to control the clinical manifestations of catecholamine release.

Adrenaline is indicated for anaphylactic reactions, and is given by injection or inhalation. Children known to be allergic to bee or wasp stings should always carry an inhaler. Alternatively, a tablet of sublingual isoprenaline (Aleudrin) may be carried. Desensitisation is possible but is usually temporary unless maintenance desensitising injections are continued indefinitely every 1–4 months.

FISH STINGS

Fish stings are a risk to holiday-makers who are relaxing in the sea, or even in freshwater where the freshwater stingray can cause problems. Venomous fish generally have bony spines covered by venom-secreting tissues and most individuals are stung when they tread on or touch a fish that possesses a venom apparatus [24]. There are a number of families of venomous species found worldwide in tropical waters. Stingrays have a flat, triangular-shaped body varying in width from a few centimetres to over 5 metres. When trodden on, the fish whips its tail, which possesses a retroserrate sting, forward. Catfish are mostly riverine, sometimes coastal, fish with serrated spines and whiskery mouthparts. Scorpionfish (Scorpaenidae) are widely distributed in tropical seas, especially around coral reefs. They have multiple dorsal spines and include *Trachinus* species (weeverfish), *Pterois* species (zebrafish, lionfish, tigerfish, etc.) and *Synanceja* (stonefish) species. Venom is injected by mechanical pressure of the victim's tissue on the venom gland around a spine.

Avoiding fish sting

If swimming or bathing in areas where such fish are known to be present, it is sensible to wear protective footwear (e.g.

'flip-flops' or plastic lightweight sandals). Care should be exercised when swimming near or touching items on sandy bottoms.

Clinical features

Stings by these fish cause an intense and often agonising local pain. Stingray injuries may cause significant lacerations and even deep puncture wounds. Systemic symptoms are generally rare in envenoming by fish, although there are reports of deaths following stonefish, zebrafish and weeverfish stings. Most species cause rapid swelling and a bluish discoloration around the sting; stonefish do not cause local necrosis, but this may be a prominent feature in weeverfish and catfish stings. Spines may becomes detached and remain embedded, leading to a chronic infection and discharge.

Treatment

The most effective treatment for the local pain of venomous fish stings is hot water, as many marine toxins are heat labile. The part stung is immersed in water as hot as the patient can bear; care must be taken to avoid burning and blistering as the severe pain may alter the sensation of the affected limb. The pain may be relieved rapidly, but continued immersion and maintenance of the temperature is necessary. Regional nerve block may be helpful and, if the part stung is unsuitable for immersion in hot water (for example, the face or trunk), the area should be infiltrated through the puncture wound with 2–5 ml of 1% lidocaine hydrochloride. Stonefish antivenom is available in Australia (only for intramuscular use) and appears to be very effective in relieving the pain. Stingray injuries may require surgical exploration and debridement.

JELLYFISH STINGS

Jellyfish have myriads of microscopic stinging capsules (nematocysts) on their tentacles. When touched, these capsules rapidly fire a sting which injects venom; however, only a small number of jellyfish have stings that can penetrate intact human skin. The most dangerous jellyfish, the box jellyfish or sea-wasp (*Chironex fleckeri*), is confined to tropical waters, mainly off the eastern coast of Australia in the region of the Great Barrier Reef and around the coasts of New Guinea (Figure 22.12). It has a cuboidal body or float, up to 200 mm in diameter, and a leash of several tentacles growing from each of the four body corners. It is translucent and difficult to see in the water. Sea-wasps of the family Chirodropidae have been found in tropical waters of all continents of the world. *Physalia* spp. ('Portuguese man-o'-war' in Atlantic waters, 'bluebottle' in Pacific waters) has a coloured float from which numerous minor tentacles hang, together with a single main tentacle that can be up to 10 metres in length. A smaller cubomedusan, *Carukia barnesi*, occurring in Indo-Pacific waters causes the 'Irukandji syndrome', so-named after an Australian aboriginal tribe.

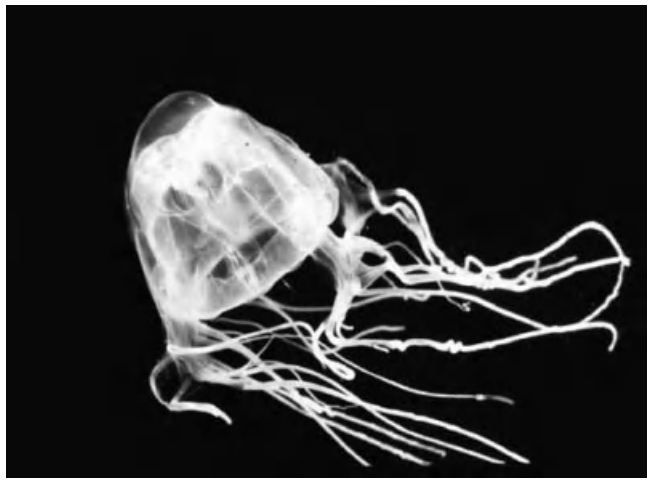

Figure 22.12 Sea-wasp or box jellyfish, *Chironex fleckeri*, the jellyfish most dangerous to humans. In its natural waters it is translucent and very difficult to see.

Avoiding jellyfish sting

If jellyfish are common on a beach, it is sensible to keep out of the water; local knowledge about safe beaches and seasons may help. In Australia, there are frequent warning signs on the beaches and special jellyfish-free areas may be cordoned off for swimmers. Protective clothing ('stinger suits') may offer some protection but cannot be relied on to prevent venomous jellyfish stings.

Clinical features

Stings by most jellyfish only cause local wheals with tingling and discomfort, usually lasting a few hours; however, a few species cause systemic syndromes which may be life-threatening. *Physalia* species have an evil reputation, but severe envenoming is relatively rare by either Atlantic or Pacific species; fatal stings are extremely rare. Long linear wheals are usually associated with severe pain which passes

off without treatment. In the Irukandji syndrome, local symptoms are minimal and the jellyfish is rarely seen. However, after 10–20 minutes, violent generalised muscle pains ensue, with restlessness, vomiting, sweating and prostration. Symptoms appear to be produced by the release of large amounts of catecholamines; severe hypertension and, rarely, cardiac decompensation can occur. Symptoms may continue for 2 days, but the sting is rarely fatal.

In contrast, a number of deaths have been recorded following stings by the box jellyfish in Australian waters. Wheals on the skin are normally multiple and 'cross-hatched'. Death can follow rapid collapse within a few minutes of the sting, probably due to myocardial toxicity, although respiratory arrest has also been recorded. Abnormal autonomic nerve activity has been observed. In non-fatal envenoming, swelling and subsequently local skin damage and necrosis can occur.

Treatment

In most jellyfish stings, only a small proportion (about 10–20%) of the nematocysts discharge their stings. This has important implications for the first aid and treatment of jellyfish envenoming. For all species, care should be taken to avoid triggering undischarged nematocysts. The stung area should not be rubbed with wet hands or a wet cloth. Liberal application of vinegar has clearly been shown to be effective in preventing the discharge of nematocysts following *Chironex* stings and is also advocated for the Irukandji syndrome. However, as there is some evidence that vinegar may cause firing of nematocysts from some *Physalia* species, these stings should be washed with sea water and adherent tentacles gently removed; hot water may provide some relief in this species [29]. In stings that are not life-threatening, pain relief is an important part of management. This may be achieved by the use of ice, but this is not effective for all species.

Although not proven to be effective, Australian authorities advocate the use of the compression-immobilisation bandaging method for severe *Chironex* stings. Artificial resuscitation on the shore may be needed; patients may develop extremely rapid envenoming after stings by this species. A potent *Chironex* antivenom is available from CSL Ltd, Australia and administration intramuscularly by first-aid teams on the beach has resulted in dramatic recovery from severe envenoming by *C. fleckeri*. Patients may require considerable intensive care support and repeated doses of antivenom in hospital [30, 31]. Although no antivenom is available for the treatment of the Irukandji syndrome, analgesia with opiates and use of alpha blockers such as phentolamine may be necessary in severe cases.

ECHINODERM STING

Stings by the spiny varieties of sea urchins are very common in travellers who may be bathing off rocky or stony beaches. They can be extremely painful, but are resolved by using the hot water treatment described above for treating fish stings. Again, the venom is heat labile and responds well to this type of therapy. Small spines, which normally break off in the victim's foot, can be left and will be absorbed after a few weeks or months. Larger spines may need to be removed to prevent infection and granuloma formation.

CONE SHELLS

These are marine snails that have evolved venoms and an elaborate harpoon-like venom apparatus. They are found particularly in Indo-Pacific waters. Their shells are attractive, leading to human envenoming when they are picked up; in some regions the snails are eaten. Those cone snails that normally hunt fish are particularly dangerous; the venom contains a mixture of neurotoxins that cause severe local pain and rapid (within 30–60 minutes) onset of profound neurotoxicity leading to respiratory paralysis and death. Management hinges on preventing absorption of the toxin by immobilisation and possibly pressure bandages and getting the victim to medical care. Antivenom is not available but supportive treatment with intubation and ventilation may be life saving. As some of the neurotoxins act postsynaptically, a trial of anticholinesterases is worthwhile, although there is no clear evidence of benefit.

Acknowledgements

We thank Professor DA Warrell, for giving permission to reproduce Figures 22.4, 22.5 and 22.6. We are also grateful to him for all his guidance, help and advice over many years.

References

1. Theakston RDG *et al.* (1977) MicroELISA for detecting and assaying snake venom and venom antibody. *Lancet* **ii**: 639–641.
2. Theakston RDG (1991) Immunological aspects of snake venom research. In: Tu AT (ed.) *Handbook of Natural Toxins*, vol. 5, *Reptile and Amphibian Venoms*, pp. 495–527. Marcel Dekker, New York.
3. Pugh RNH and Theakston RDG (1980) The incidence and mortality of snake bite in savanna Nigeria. *Lancet* **ii**: 1181–1183.
4. Larrick JW *et al.* (1978) Snake bite among the Waorani Indians of eastern Ecuador. *Trans Roy Soc Trop Med Hyg* **72**: 542–543.

5. Phillips RE *et al.* (1988) Paralysis, rhabdomyolysis and haemolysis caused by bites of Russell's viper (*Vipera russelli pulchella*) in Sri Lanka: failure of Indian (Haflkine) antivenom. *Q J Med* **68**: 691–716.
6. Virivan C *et al.* (1986) ELISA confirmation of acute and past envenoming by the monocellate Thai cobra (*Naja kaouthia*). *Am J Trop Med Hyg* **35**: 173–181.
7. Warrell DA *et al.* (1986) Randomized comparative trial of three monospecific antivenoms for bites by the Malayan pit viper (*Calloselasma rhodostoma*) in southern Thailand: clinical and laboratory correlations. *Am J Trop Med Hyg* **35**: 1235–1247.
8. Kasturiratne A *et al.* (2008) The global burden of snakebite: A literature analysis and modelling based on regional estimates of envenoming and deaths. *Public Library Sci Med* **5**: 1–14.
9. Lalloo DG *et al.* (1995) Snakebites by the Papuan Taipan (*Oxyuranus scutellatus canni*): paralysis, haemostatic and electrocardiographic abnormalities and effects of antivenom. *Am J Trop Med Hyg* **52**: 525–531.
10. Sano-Martins IS *et al.* (1994) Reliability of the simple 20 minute whole blood clotting test (WBCT20) as an indicator of low plasma fibrinogen concentration in patients envenomed by *Bothrops* snakes. *Toxicon* **32**: 1045–1050.
11. Warrell DA *et al.* (1977) Poisoning by bites of the saw-scaled or carpet viper (*Echis carinatus*) in Nigeria. *Q J Med* **46**: 33–62.
12. White J (1987) Elapid snakes: management of bites. In: Covacevich J *et al.* (eds) *Toxic Plants and Animals. A Guide for Australia*, pp. 431–457. Queensland Museum, Brisbane.
13. Theakston RDG *et al.* (1990) Bacteriological studies of the venom and mouth cavities of wild Malayan pit vipers (*Calloselasma rhodostoma*) in southern Thailand. *Trans Roy Soc Trop Med Hyg* **84**: 875–879.
14. Cardoso JLC *et al.* (1993) Randomized comparative trial of three antivenoms in the treatment of envenoming by lance-headed vipers (*Bothrops jararaca*) in São Paulo, Brazil. *Q J Med* **86**: 315–325.
15. Theakston RDG *et al.* (2003) Report of a WHO workshop on the standardization and control of antivenoms. *Toxicon* **41**: 451–457.
16. WHO (2010) Guidelines for the production, control and regulation of snake antivenom immunoglobulins. Expert Committee on Biological Standardization, Geneva.
17. Theakston RDG and Smith DC (1995) Therapeutic antibodies to snake venoms. In: Landon J and Chard T (eds) *Therapeutic Antibodies*, pp. 109–133. Springer-Verlag, New York.
18. Meyer WP *et al.* (1997) First clinical experiences with a new ovine Fab *Echis ocellatus* snakebite antivenom in Nigeria: randomised comparative trial with Institute Pasteur serum (Ipser) Africa antivenom. *Am J Trop Med Hyg* **56**: 291–300.
19. Gutierrez J-M *et al.* (2005) Pan-African polyspecific antivenomproduced by caprylic acid purification of horse IgG: an alternative to the antivenom crisis in Nigeria. *Trans Roy Soc Trop Med Hyg* **99**: 468–475.
20. Abubakar IS *et al.* (2010) Pre-clinical and preliminary dose-finding and safety studies of new antivenoms for treating envenoming by the saw-scaled or carpet viper (*Echis ocellatus*) in Nigeria. *Toxicon* **55**: 719–723.
21. Abubakar IS *et al.* (2010) Randomised, double-blind controlled trial of two new antivenoms for treating envenoming by the saw-scaled or carpet viper (*Echis ocellatus*) in Nigeria. *PLos NTD* **4**: 1–10.
22. Isbister GK *et al.* (2009) Failure of antivenom to improve recovery in Australian snakebite coagulopathy. *Q J Med* **102**: 563–568.
23. Malasit P *et al.* (1986) Prediction, prevention and mechanism of early (anaphylactic) antivenom reactions in victims of snake bites. *Br Med J* **292**: 17–20.
24. Warrell DA (1983) Injuries, envenoming, poisoning, and allergic reactions caused by animals. In: Weatherall DJ *et al.* (eds) *Oxford Textbook of Medicine*, vol. 1, *Chemical and Physical Injuries, Climatic and Occupational Diseases*, pp. 6.35–6.47. Oxford University Press, Oxford.
25. Premawardhena AP *et al.* (1999) Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. *Br Med J* **318**: 1041–1043.
26. De Silva HA *et al.* (2011) Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. *PLoS Med* **8**: e1000435.
27. WHO (1981) *Progress in the Characterization of Venoms and Standardization of Antivenoms*, WHO Offset Publication No.58. World Health Organization, Geneva.
28. França FOS *et al.* (1994) Severe and fatal attacks by 'killer bees (Africanized honey bees—*Apis mellifera scutellata*) in Brazil: clinicopathological studies with measurement of serum venom concentrations. *Q J Med* **87**: 269–282.
29. Loten C *et al.* (2006) A randomised controlled trial of hot water (45°C) immersion versus ice packs for pain relief in bluebottle stings. *Med J Australia* **184**: 329–333.
30. Fenner PJ (1998) Dangers in the ocean: the traveler and marine envenomation. I. Jellyfish. *J Travel Med* **5**: 135–141.
31. Fenner PJ (1998) Dangers in the ocean: the traveler and marine envenomation. II. Marine vertebrates. *J Travel Med* **5**: 213–216.
32. Theakston RDG and Warrell DA (1991) Antivenoms: a list of hyperimmune sera currently available for the treatment of envenoming by bites and stings. *Toxicon* **29**: 1419–1470.
33. Meier J and White J (1995) *Handbook of Clinical Toxicology of Animal Venoms and Poisons*. CRC Press, New York.

Additional resources

Some institutes making antivenom. For a more complete list see Theakston and Warrell [32] and Meier and White [33].

1 *Algeria.* Institut Pasteur d'Algeria, Rue Docteur Laveran, Algiers.

2 *Argentina.* Instituto Nacional de Microbiologia, Av. Velez Sarsfield 563, Buenos Aires.

3 *Australia.* CSL Ltd, 45 Poplar Road, Parkville, Victoria 3052.

4 *Brazil.* (a) Instituto Butantan, Caixa Postal 65, São Paulo.

5 (b) Fundacão Ezequiel Dias, Rua Conde Pereira Carneiro 80, Belo Horizonte.

6 *Burma (Myanmar).* Industrie & Pharmaceutical Co., Rangoon (Yangon).

7 *China.* Shanghai Vaccine and Serum Institute, 1262 Yang An Road (W), Shanghai.
8 *Colombia.* Instituto Nacional de Salud, Av. Eldorado con Carrera, Zona G, Bogota.
9 *Costa Rica.* Instituto Clodomiro Picado, San Jose.
10 *Croatia.* Institute of Immunology, Rockerfellerova 2, Zagreb.
11 *Czech Republic.* Institute of Sera and Vaccines, W. Pieeka Str. 108, 10 103 Prague 10.
12 *Ecuador.* Instituto Nacional de Higiene y Medicina Tropical, Casilla Postal 3961, Guayaquil.
13 *Egypt.* Al Algousa Sharea, Alvezara, Cairo.
14 *France.* Sanofi Pasteur SA, Av Pont Pasteur 2, cedex 07, 69367, Lyon.
15 *Germany.* Knoll Pharmaceuticals, Postfach 21 08 05, Ludwigshafen.
16 *India.* (a) Central Research Institute, Kasauli, R.I., Punjab.
17 (b) Haffkine Bio-Pharmaceutical Corporation, Parel, Bombay 12.
18 (c) Serum Institute of India, 212/2 Hadaspar, Pune–411 028.
19 *Indonesia.* Perusahaan Negara Bio Farma, 9 Djalan Pasteur, Bandung.
20 *Iran.* Institut d'Etat des Serums et Vaccins Razi, Boite Postale 656, Tehran.
21 *Israel.* Ministry of Health, POB 6115, Jerusalem 91060.
22 *Italy.* Instituto Sieroterapico Vaccinogeno, Via Fiorentina 1, 53 100 Siena.
23 *Japan.* Takeda Chemical Industries Ltd, Osaka.
24 *Morocco.* Institut Pasteur, Place Charles-Nicolle, Casablanca.
25 *Pakistan.* National Institute of Health, Islamabad.
26 *Peru.* Instituto Nacional de Salud, Calle Capac Yupanqui 1400, Lima.
27 *Philippines.* Serum and Vaccine Laboratories, Alabang Multinlupa, Rizal.
28 *Russia.* Ministry of Public Health, 101 431, GSP 4, Moscow K–51.
29 *South Africa.* South African Institute for Medical Research, PO Box 1038, Johannesburg 2000.
30 *Switzerland.* Institut Serotherapique et Vaccinal Suisse, CP 2707, 3001 Berne.
31 *Taiwan.* National Institute of Preventive Medicine, 161 Kun Yang St., Taipei.
32 *Thailand.* Thai Red Cross, Queen Saovabha Memorial Institute, Bangkok.
33 *Tunisia.* Institut Pasteur, 13 Place Pasteur, Tunis.
34 *USA.* (a) Arizona State University, Temp, Arizona 85287–2701.
35 (b) Protherics, 5214 Maryland Way, Suite 405, TN 37027, Brentwood, USA.
36 (c) Merck, Sharp and Dohme Int., POB 2000, Rahway, NJ 07065.
37 *West Africa.* Micropharm Ltd, 14–15 Newbury Street, London EC1A 7HU, UK.

Scorpion antivenoms are made at institutes 1, 4, 10, 15, 16, 20, 24, 29 and 33; spider antivenoms at institutes 3, 4, 20, 26, 29 and 37; jellyfish (sea-wasp) at institute 3; and fish antivenoms at institutes 3 and 10.

Doctors who need supplies of antivenom for use in various geographical areas may find the following most useful.

Americas: polyvalent viper antivenom from 2, 4, 5, 8, 9, 12 or 26; coral snake antivenom from 2, 4, 5, 9 or 26.
North Africa: viper antivenom from 1, 13, 14, 20, 21, 24, 29 or 33.
Mid-Africa: polyvalent antivenom from 14 or 29.
South Africa: polyvalent antivenom from 29.
Middle East: viper-cobra antivenom from 14 or 20.
Asia: (sea snake bite) sea snake or tiger snake antivenom from 3.
India and Pakistan: cobra-krait-viper antivenom from 16, 17, 18 or 25.
Burma (Myanmar): cobra-viper antivenom from 6.
Cambodia, Laos, Malaysia, Vietnam, Thailand: viper and cobra antivenoms from 32.
Indonesia: cobra-krait-viper antivenom from 19.
Japan: viper antivenom from 23.
Philippines and Taiwan: cobra-krait-viper antivenom from 31.

Chapter 23 Ophthalmic conditions in travellers

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Sunlight exposure

The eye is the only organ, apart from the skin, that is directly exposed to radiation from the sun. Biologically, the most damaging wavelengths encountered are ultraviolet B (UVB) and, to a lesser extent, ultraviolet A (UVA) and blue light.

Ten per cent of all light energy reaching the earth's surface is ultraviolet light. Ninety per cent of this is UVA (400–320 nm). Most of the rest is longer wavelengths of UVB (320–280 nm). Ultraviolet C (UVC), the shortest wavelength light and shorter wavelengths of UVB, is normally filtered by the ozone layer and the upper atmosphere. There has been a 3–6% per decade decrease in the ozone layer, resulting in an increase of ultraviolet light reaching the earth's surface, particularly in Antarctica.

Vulnerability to ultraviolet light damage

Youth

With age, protection is afforded from sunlight by overhanging eyelid skin, bushier eyebrows, relative corneal opacification, smaller pupils and increasing absorption of shorter wavelengths by the lens, which protects the retina from ultraviolet and blue light. Young people spend more time outdoors than the elderly.

Pigmentation

Lightly pigmented individuals are more at risk from sunburn, basal cell carcinoma of the eyelids and age-related macular degeneration.

Occupation

Ocular exposure to ultraviolet light is related to occupation. The Maryland waterman study showed a 20-fold difference of exposure to ultraviolet light between men who worked on deck and those who worked inside the boats.

Eyelid damage

Sunburn

Sunbathing can result in unpleasant, but rarely dangerous, sunburn to the eyelids. Beach umbrellas and hats provide limited protection due to the reflection by sand and water.

Chronic lid exposure

Superficial keratosis, age spots, comedones, sebaceous hyperplasia, blepharitis (Figure 23.1), premalignant and malignant lesions are all more likely where there is or has been chronic exposure to ultraviolet light.

Malignant tumours

Actinic keratosis is a premalignant squamous change seen in the eyelids. Basal cell carcinomas (Figure 23.2) are common in Caucasians living in sunny countries such as Australia and South Africa. Both these countries have vigorous education campaigns, such as the 'No hat, no play' rule for school children. Squamous cell carcinoma is rarer than basal cell carcinoma. Malignant melanoma of the lids is very rare and constitutes well under 1% of all malignant lesions of the eyelids. All these conditions are related to ultraviolet light exposure.

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

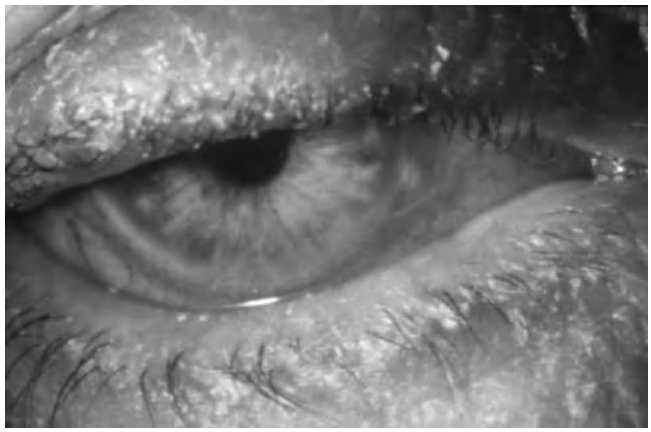

Figure 23.1 Blepharitis.

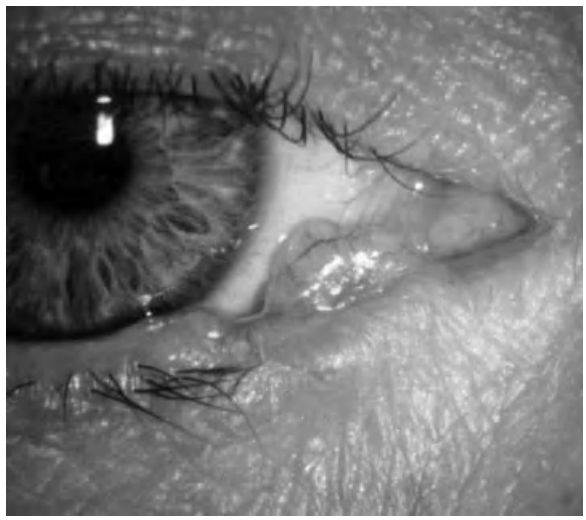

Figure 23.2 Lower lid basal cell carcinoma.

Cornea and conjunctiva

Damage to the cornea by ultraviolet light is both intensity- and wavelength-dependent.

Acute keratitis

UVC and very short wavelength ultraviolet light of 260–290 nm are maximally absorbed by the corneal proteins. Even a brief exposure can cause an acute keratitis (inflammation of the cornea). In practice, this is mostly seen as an effect of a welder's flash. The person develops very painful, photophobic, red and watery eyes 4–10 hours after the exposure. This lasts for 12 hours, with some residual discomfort for 2–4 days. Time and reassurance is the mainstay of treatment. It is reasonable to instill local anaesthetic drops to help the patient sleep, but these should not be used more than twice as there is a risk of delayed healing and of unnoticed trauma. Antibiotics are not needed.

Sunbeds can be a risk, especially those of an older variety that emit UVB as well as UVA. UVA does not cause acute keratitis but is implicated in pterygia and cataract.

Chronic keratitis

Climatic droplet keratopathy and Labrador keratitis are names for chronic exposure to ultraviolet radiation that results in yellow or golden subepithelial oil-like droplets in the cornea, which are initially clear but later become opaque, spreading from the periphery of the cornea to the centre. It is seen predominantly in the Inuit in northern Canada and in Arab desert dwellers. Males are typically affected more than females.

Pingueculum

This is an elastotic degeneration of the conjunctiva and is frequently seen in elderly people and probably due to cumulative damage to the conjunctiva by ultraviolet light.

Pterygium

Pterygium is the growth of a fibrovascular membrane from the conjunctiva and which affects typically the nasal side of the cornea. It is more common with exposure to sunlight, proximity to the equator and in windy countries, suggesting that mechanical abrasion is a factor in its development. It is therefore seen particularly in coastal areas and in desert people. Pterygia seem to develop many years after exposure: this is particularly evident, for instance in the UK, where West Indians immigrating in early adulthood do not develop their pterygia until years later, living in less than sunny Britain.

Pterygia are unlikely to be sight threatening in travellers and are likely only to cause chronic mild discomfort and to be cosmetically disfiguring. Surgery for pterygia is usually done for cosmetic reasons. Unfortunately, it is complicated by recurrences. The currently favoured surgical technique to avoid recurrence is to remove the pterygium and then place a free conjunctival graft between the conjunctiva and the cornea.

Cataract

A cataract is an opacification of the lens and the prevalence increases with age. There are, however, great differences in prevalence between countries. Although population surveys

are difficult to compare because of differing definitions of cataract, there is a greater incidence and prevalence in Asia compared with Britain (between four- and tenfold in most age groups). Sunlight exposure, diabetes, diarrhoea, alcohol and cigarette smoking are all strongly associated with cataracts.

Protection from sunlight exposure

Appropriate eye protection is important in preventing the conditions described above.

Hats and sunglasses should be worn during long periods in the sunshine, especially at the beach and when engaged in water sports.

Dark glasses

On a sunny day, the high light levels saturate the retina and reduce overall visual performance, particularly distinguishing between fine levels of contrast in objects of similar colour and shade. Most sunglasses will absorb 70–80% of incident light of all wavelengths and will improve visual function.

Polaroid sunglasses reduce glare from reflective light from the road or water. Wide sunglasses that curve around the eyes reduce glare from the side.

Photochromic lenses darken when exposed to short wavelength light; they may be made of glass or plastic. In the case of glass, there is a chemical reaction of conversion of silver ion to elemental silver. The reaction is reversible when the glass is returned to the dark. At its most dark, about 80% of the light is absorbed, and at its most light about 20% of light is absorbed. It takes longer for the glass to lighten than it does for it to darken.

Plastic photochromic lenses depend for their property on a chemical coating that lightens and darkens with exposure to short wavelength light. The chemical coating is more easily damaged than that of the glass lenses.

Blue lenses are much less effective at absorbing short wavelength light than are lenses of other colours and should not be used.

Aircraft travel and the eye

In an aircraft the eye is exposed to an atmosphere that is drier and under lower pressure than normal. In addition, there are often air vents above seats that cause increased evaporation of tears. Travellers often cannot sleep on long-haul flights and will attempt to pass the time by reading, using their computers and watching movies. When people are tired their rate of blinking also decreases. This combination of conditions can aggravate existing eye problems as well as give rise to symptoms in people who do not ordinarily suffer from dry eyes.

Dry eye

It is estimated that almost 5 million Americans aged 50 years or over suffer from dry eye, with female sufferers outnumbering males by a ratio of 2:1 [1]. Many more people have less severe symptoms that only become apparent in low humidity conditions such as in an aircraft.

It is advisable for susceptible travellers to take artificial tears with them, which can easily be bought over the counter at most pharmacies. A range of products is available, and different preparations should be tried before travelling to see which is most suitable. Drops should be used frequently during the flight.

Management

If eyes become dry, red or gritty, it will help if the vents above the seats are turned off. Artificial teardrops should be used when the eyes feel dry, as often as every 15 minutes. Those with severe dry eye or who are sensitive to preservatives can use preservative-free drops.

Recurrent corneal erosion

Many people who have had previous corneal abrasions may experience a recurrence, especially in conditions of low humidity and dry ocular surface such as on an aircraft. This presents with a sudden onset of pain, watering and photophobia, usually on waking or after minor trauma. Treatment is the same as for a corneal abrasion by applying an antibiotic ointment four times a day. To prevent the pain recurring, patients are advised to make liberal use of lubricating eye drops during the flight, and also to use simple eye ointment before sleeping.

Following eye operations

It is generally safe to travel by air after a short period of convalescence following most eye operations, including for squints, cataracts, glaucoma, corneal grafts and after laser treatment for diabetic eye disease.

Following retinal detachment surgery the surgeon will advise whether or not it is safe to fly in the convalescence period. It depends on whether intraocular gases such as air, SF6 or C3F8 were used during surgery. Due to the lower cabin pressure, these intraocular gases will expand and cause

a dangerous rise in intraocular pressure. Patients who have had C3F8 have to wait about 6 weeks to allow absorption of the gas. In the case of air, 2–3 days is usually sufficient, and with SF6 2–3 weeks.

Accidental injuries could occur when a patient has had cataract surgery and the vision is still not clear. These patients are more susceptible to bumping their face and operated eye when travelling, especially when attempting to load the overhead luggage rack. It is therefore advisable to wear an eye shield for the transit periods in the first few postoperative weeks. These can be of clear acrylic material.

Diabetic retinopathy

Patients who need treatment for diabetic eye disease should finish the course of treatment prior to travel. There is no evidence that vitreous haemorrhages are more likely during aircraft travel. Trauma should be avoided. People who have diabetes need to continue good control of the diabetes despite the variation in diet, daily routine and jet lag. Blurring of vision can occur during hypoglycaemic attacks.

Changes in refractive error complicate variable glucose levels.

Ocular changes at altitude

Most visual problems at altitude are related to exposure of the corneas to wind, cold and ultraviolet light. Wind and cold cause mechanical abrasions and drying of the cornea. Ultraviolet light damage causes snow blindness.

Snow blindness

Damage to the corneal epithelial layer can occur on exposure to UV light at high altitudes. The amount of UV light falling on the cornea is increased by reflection off the snow surface. Actual blistering of the cornea can occur, with intense congestion of the conjunctiva. Corneal ulceration can result and these areas will stain with fluorescein drops.

Symptoms of photophobia and pain resulting in the inability to open the eyes typically occur a few hours after exposure. In an emergency, the pain and blepharospasm can be treated with anaesthetic drops but continuous use is not advised as corneal healing is impeded. Application of an antibiotic ointment and lubricants is advisable and the corneal surface should heal in a few days.

Mountaineers are reminded that extreme precautions against exposure to ultraviolet light and wind damage must be taken, with purpose-made glacier glasses or goggles that protect from the side as well.

High-altitude retinopathy

Retinal examinations of people climbing on Everest expeditions have shown the common occurrence of dilated retinal veins, pre-retinal and intra-retinal haemorrhages. This is more so when higher altitudes are reached. The majority of these are not sight threatening and will resolve after descent to low altitude. However, despite being a benign condition, advancing high-altitude retinopathy may predict the onset of high-altitude cerebral oedema, which can be lethal if immediate descent is not undertaken [2].

Contact lens wear at high altitude

This is permitted, however the risk of infection is potentially greater as one may find it difficult to adhere strictly to good hygienic measures.

Refractive surgery and high altitude

A change in refractive state can occur on ascent to high altitude in individuals who have previously had corrective surgery.

This change is temporary and reversible on return to sea level. Refractive shifts, particularly hyperopic shifts, occur more commonly in eyes that have undergone radial keratotomies when compared with LASIK. It is also thought that eyes that had previous LASIK corrective surgery can tolerate higher altitudes; even up to 26,000 feet before fluctuation of vision occurs [3].

Diving

SCUBA diving is a recreational activity that is popular with travellers. A diver should have good vision to enjoy the beautiful underwater sights, and near vision to read the gauges and timer so as not to overstay their time underwater.

If wearing contact lenses, the fit should be comfortable prior to the dive. Soft lenses are preferable. Specially made prescription facemasks are an alternative.

Ocular barotrauma

Prior to diving, the diver should ensure that the facemask has a snug fit over the face. This prevents water from entering the eyes and nose; however, the volume of air in the facemask becomes compressed during descent, hence a relative negative pressure develops in this space. Barotrauma can occur when the tissues of the eye and its surroundings are drawn into the mask with resultant bruising and swelling of the

eyelids, and subconjunctival haemorrhages. These injuries are unsightly but will resolve in a week or two. In order to prevent barotrauma, the diver must breathe into the face-mask when descending.

Individuals who have recently undergone ocular surgery with intraocular gas are also at risk of barotrauma. This can occur because the gaseous volume decreases on diving, the consequences of which can be disastrous. The contents of the eye can cave in and this will result in irreversible damage to the eye. Gas is commonly used during vitreo-retinal operations and individuals should check with their operating surgeon with regard to the specific convalescence time.

Gas embolism

This may occur as a result of pulmonary barotrauma or decompression sickness. Pulmonary barotrauma occurs when the lining of the lung is breached as the air held inside expands on ascent. This causes bubbles to form in the pulmonary circulation and these are disseminated systemically. Decompression sickness occurs when air bubbles form from a dissolved state due to pressure differences encountered on ascent.

Decompression sickness can give rise to ophthalmic symptoms such as decreased visual acuity, diplopia and visual field defects. Common symptoms are joint pain, skin mottling, headaches, weakness, tingling in the limbs, cranial nerve palsies and loss of consciousness.

Arterial gas embolism as a consequence of pulmonary barotrauma can give rise to neurological symptoms similar to those of decompression sickness as the blood circulation to the brain is affected. In addition, a central retinal artery occlusion may result from an arterial gas embolus, which presents itself as a sudden loss of vision.

In general, the timely diagnosis of decompression sickness or arterial gas embolism is crucial in order to provide emergency recompression treatment and hyperbaric oxygen.

Convalescence period following ophthalmic surgery

Sufficient time is necessary for the surgical wounds to heal before diving.

Diving is contraindicated when intraocular gas is used until resorption has occurred, and when hollow implants have been placed into the orbit.

It is advisable to undergo a postoperative check prior to diving. The diver can seek advice from the treating ophthalmologist with regard to the prevention and risk of potential complications.

Table 23.1 provides guidance to minimum convalescence periods. Reference [4] is recommended as further reading.

Table 23.1 Recommended minimum convalescent periods prior to diving after ophthalmic surgery

Procedure		Recommended minimum convalescent period
Anterior segment surgery	Penetrating keratoplasty	6 months
	Corneal laceration repair	6 months
	Cataract surgery	1–3 months depending on type of incision made
	Radial keratotomy	3 months
	Photorefractive keratectomy	2 weeks
	LASIK	1 month
	Pterygium excision	2 weeks
	Conjunctival surgery	2 weeks
	Corneal suture removal	1 week
Glaucoma surgery	Glaucoma filtering surgery	2 months (relative contraindication to diving)
Vitreo-retinal surgery	Retinal detachment repair	2 months
	Pneumatic retinopexy	2 months (diving contraindicated until intraocular gas resorbed)
	Vitrectomy	2 months (diving is contraindicated until intraocular gas resorbed)
	Retinal cryopexy or laser photocoagulation for retinal breaks	2 weeks
Oculoplastic surgery	Sutured wound	2 weeks
	Skin graft or granulating wound	Until epithelialisation is complete
	Enucleation	2 weeks (diving contraindicated with hollow orbital implants)
Strabismus surgery		2 weeks

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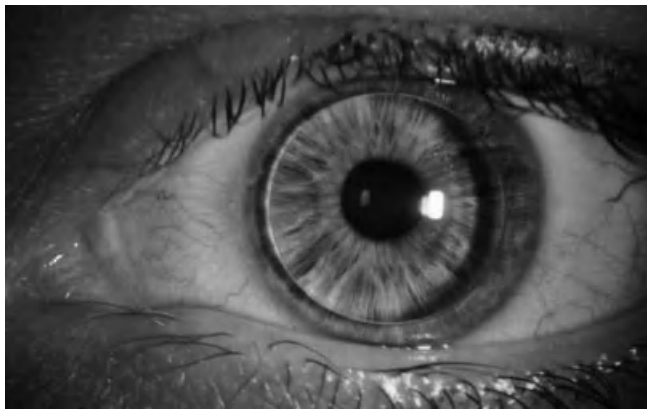

Figure 23.3 Hard contact lens.

The red eye

A full discussion of the management of a red eye that may occur coincidentally in a patient who is travelling is beyond the scope of this chapter, and the reader is referred to a standard ophthalmic textbook. However, as a rule of thumb if the eye is painful and the vision is significantly decreased then expert medical attention should be sought.

Contact lens wear

Contact lens type

Contact lenses are favoured by some people to correct refractive errors. There are two basic types of contact lens: hard (Figure 23.3) and soft.

Hard lenses

These are rigid, and are made of either polymethylmethacrylate or a gas-permeable material. They are less likely than soft lenses to lead to ulcers because they do not sequester bacteria. However, they can be uncomfortable to wear and require adaptation.

Soft contact lenses

These can be further divided.

- *Extended wear lenses.* These are rarely prescribed routinely but may be used in patients with other ocular problems. Wearers are more likely to suffer infection owing to poor oxygen penetration to the cornea, and the lack of regular cleaning of the lenses.
- *Two-weekly/monthly lenses.* These soft contact lenses can be worn daily for up to a month (or as prescribed) and must be removed and cleaned each night with the prescribed solution.
- *Daily wear lenses.* A fresh new pair is worn each day and then discarded.

Concerns with contact lens wear while travelling

The wearing of contact lenses is hazardous alone, without adding the extra factor of travelling. The contact lens can sequester bacteria on its surface, forming a unique biofilm. This must be removed daily to prevent infection taking hold, which can happen when the corneal epithelium is breached. Poor hygiene and overwear may lead to corneal epithelial breakdown, resulting in the development of a bacterial corneal ulcer. Long flights and a dry atmosphere increase the risk of dry eyes and corneal ulcers.

Travelling disrupts the daily routine of contact lens care, which involves cleaning, sterilising and deproteinising of the lens, and proper storage.

Flying to and from different time zones makes estimating the duration of contact lens wear and its care more difficult. It is important to wash hands thoroughly before touching the lens, but facilities when travelling may be suboptimal. In such circumstances the normal routine is skimped.

Some travellers may even leave their contact lens in overnight despite being advised against doing so.

Related corneal abrasions

Inadvertent corneal abrasions with fingernails can occur, especially when removal is made more difficult due to overwear, or in cases where the atmosphere is drier, due to the lens sticking fast to the cornea. Abrasions can also occur when careless attempts at removal are made without using a mirror (in the inexperienced). The contact lens can snap and the remnant left behind in the eye may be even more difficult to remove.

Low humidity levels in an aircraft

The low-humidity environment in an aircraft leads to drying of contact lenses when worn in-flight. This gives rise to a sense of grittiness or discomfort. It is advisable not to wear contact lenses on long-haul flights; however, if this cannot be avoided then ocular lubrication should be used throughout the flight to ensure that the lenses are kept moist. Individuals are advised to check that their eye lubricant of choice is compatible with contact lens wear.

Practical steps to reduce infection risk

The monthly disposable lens is associated with the greatest risk of corneal ulcer. Due to expense or convenience, wearers may be unwisely tempted to extend the life of the lens for over a month, especially in the case of younger travellers. Travellers should consider changing to daily disposable lenses for the duration of the holiday. Meticulous hand hygiene is necessary when handling contact lens.

The traveller should have a spare lens storage case as backup, and a new one for each month of travel. These should be air-dried when lenses are being worn, and fresh disinfecting solution must be used for each episode. Only sterile solutions should be used to store or wash lenses or cases.

Contact lens sterilising solutions, where there is less than ideal hygiene, should contain hydrogen peroxide, which eradicates acanthamoeba cysts. Travellers should carry solutions, as similar products are often unobtainable abroad. A new bottle should be used for each month, as open bottles can soon become contaminated.

In addition, travellers should be mindful of restrictions on liquids brought onto aircrafts, and should ensure that all eye drops and ointments brought onto the flight comply with applicable size requirements and are carried in a clear plastic bag to facilitate security screening. Travellers should check with their airlines for information regarding the most up-to-date requirements for liquids on board the aircraft. In addition, one must exercise caution when decanting solution into unlabelled bottles as a mix up can easily occur that can lead to a nasty chemical injury.

Travellers are advised to seek medical advice if ocular redness, pain or blurred vision occurs because of the risk of corneal ulcer (Figure 23.4). If unable to do so, the traveller is to immediately discontinue contact lens use and consider precautionary use of topical antibiotics (e.g. hourly ofloxacin eyedrops) until proper medical advice is obtained.

In every case, glasses should be carried as a backup. Some opticians run insurance schemes that guarantee next-day delivery of replacement lenses or glasses to most parts of the world. Do carry adequate solutions, cases and spare glasses in the hand luggage in case checked baggage is lost.

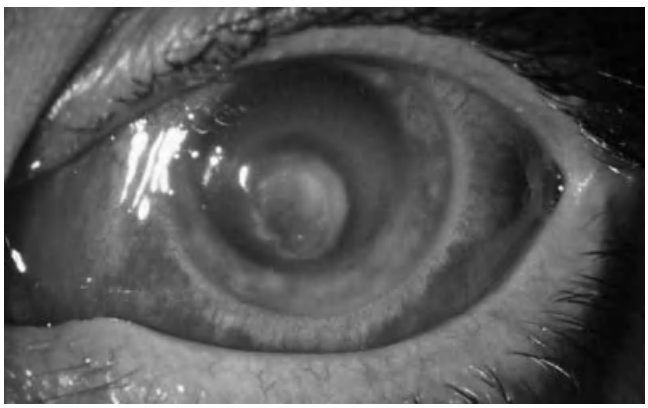

Figure 23.4 Corneal ulcer.

Trauma

Corneal abrasion

Fingernail or twig injuries usually cause corneal abrasions. Corneal epithelial defects will show as a yellow area if fluorescein is instilled and light from a pen torch with a blue filter is shone on it. Anaesthetic drops aid the examination.

Treatment

An antibiotic ointment should be used four times a day for 5 days. Cyclopentolate 1% twice a day can reduce ciliary spasm and pain. Ketorolac (Acular) drops may help. Oral analgesics can be taken. Avoid regular use of topical anaesthetics as they slow the healing process.

Fungal ulcers are common where trauma is due to organic matter, particularly in agricultural areas of India and Australia.

Corneal foreign body removal

A superficial foreign body may be removed with topical anaesthetic and a 21 gauge needle; the cornea is tough and is reasonably difficult to perforate. Deeply embedded foreign bodies should be removed by a specialist at a slit lamp. Leaving a rust ring can lead to a chronically uncomfortable eye.

Major trauma

Inadequate diagnostic facilities can pose difficulties when travelling. A decision may need to be made as to whether the patient should be transferred to a centre for assessment and surgical treatment.

Severe trauma to the eye can occur in traffic accidents. Unfamiliar roads, driving on the opposite side, different road rules, unfamiliar car controls and poorly serviced vehicles when driving a hired car can lead to an increased risk of accidents. The relaxed holiday-maker may forget about wearing seat belts.

Penetrating injuries

These can occur with sharp objects that hit the eye at sufficient speed and force. Check the visual acuity and examine the eye carefully with a torch. Subconjunctival haemorrhages can hide an underlying scleral laceration.

If vision is affected, look carefully at the pupil for irregularity or for a teardrop-shape. The iris is often sucked into the wound site if the cornea is perforated. You will need to be very careful to prevent further prolapse of ocular contents. Gently separate the eyelids to examine the eye. Cotton buds can be used to facilitate the examination.

Management of penetrating injuries Tetanus status should be sought and prophylaxis given as necessary. Apply an eye shield. Oral antibiotics such as ciprofloxacin should be initiated, as well as analgesia and antiemetics if necessary. Transfer to hospital is required for further examination and surgical wound closure, which should be performed on an emergent basis.

The need for repatriation depends on the availability of expertise and equipment locally. Good ophthalmic services can be found in most large cities in the Far East and India, all of Europe, the US and Russia.

A study [5] looking at prognostic factors in corneoscleral lacerations found that a delay of up to 36 hours in performing the initial repair had no effect on the final outcome.

However, endophthalmitis can develop if wound closure is delayed. It can be more common if the injuries are sustained in rural settings with contamination from organic matter [6], or if there is foreign body retention [7]. Not all studies agree on the odds and timing of this so it is advisable to have the injury repaired as soon as safely possible and in centres where technical expertise is present.

Intraocular foreign body (IOFB)

A foreign body can be retained within the eye with penetrating eye injuries from high-velocity missile injuries such as drilling, hammering, etc. The entry site into the eye may not always be obvious. Never ignore the patient who tells you there is something floating in their vision following an ocular accident. Small thin shards of metal or glass can penetrate the cornea and lens or zonules with hardly a trace. Retained metal foreign bodies can be toxic to the eye. A high index of suspicion is necessary. Always take a full history and conducting a careful examination with the pupil dilated. Radiological imaging can be performed to look for IOFBs; however, not all will show up. These foreign bodies will need to be removed by special vitrectomy procedures.

Blunt injury

Blunt injury can result in hyphaema, dislocated lens, retinal detachment, commotio retinae, vitreous detachment and haemorrhage. Trauma can also result in orbital wall fractures.

Hyphaema

Hyphaema is a bleed into the anterior chamber of the eye. Sometimes in a severe bleed the entire anterior chamber fills up with blood. The blood originates usually from a tear in the iris or iris root.

Management of hyphaema The vision will be clearer if the patient maintains a head-up position as the bleed will settle, resulting in the formation of a blood level. If the patient is on aspirin, it may be better to stop it temporarily. Check for an associated corneal abrasion if there is severe pain. If dilation is performed, cyclopentolate 1% drops should be instilled three times a day. Topical steroids, e.g. dexamethasone 0.1% eye drops four times a day, can reduce intraocular inflammation. Corneal haziness may indicate raised intraocular pressure so one or two tablets (250–500 mg) of acetazolamide (Diamox) will reduce the pressure and relieve pain.

A follow-up with an ophthalmologist must be arranged as soon as possible to verify the diagnosis, monitor the treatment and to check whether any other injury has occurred or whether there is damage to the drainage angle. The individual is a risk of developing glaucoma even as late as 20 years after the initial event, more so if there is greater than 50% damage to the drainage angle. Annual clinic or optometrist review is warranted.

Flashers and floaters following blunt injury: retinal detachment or not?

Patients who have experienced a blow to the eye may not notice any symptoms initially. After a few days, flashing lights or floaters in the vision may signal the development of a posterior vitreous detachment. This does not always mean there is a retinal detachment or tear, but a dilated examination of the retina is necessary. A constant shadow in the field of vision may be due to a retinal detachment. Retinal detachments can occur spontaneously without preceding trauma. A good central vision does not exclude a detachment.

Urgency of retinal detachment repair The shorter the duration of symptoms the more urgent the repair is. This is especially so if the macula is not detached and can be ascertained from the history (central visual acuity is not impaired)

and fundal examination. One should act quickly in these cases and plan for emergent repatriation and surgery.

Poor vision (6/60 or less) may indicate macula involvement.

In general, arrangements should be made for urgent repair; however, for macular off detachments, a delay of up to a week from the onset may not necessarily jeopardise outcome [8].

If access to a modern vitreo-retinal service is not available, repatriation is probably best. If the diagnosis of a superior retinal detachment is made, it is probably better that the patient be transported in a prone position to prevent further peeling of the neurosensory retina. This is because fluid can enter the tear in the detachment and, by gravity, increase the detachment. A prone position is achieved by lying on the tummy face down or in the sitting position, e.g. on an aircraft face down with the head resting on a pillow on the lap or the table in front.

Orbital fracture

Fracture to the walls of the orbit commonly occurs from missiles such as a golf, tennis and squash balls. They also occur in fights between drunk and disorderly travellers.

It is important to perform a thorough ophthalmological examination, including looking for any reduction in eye movements; specifically check visual acuity and for a relative afferent papillary defect as the eye or the optic nerve can be damaged concurrently or as a consequence of the fracture.

The signs and symptoms will vary according to the orbital wall that is fractured. The fracture that is often missed is the orbital floor fracture or blow-out fracture, sustained by direct impact on the globe, for example from a ball or fist. The force is transmitted from globe to delicate bone of the orbital floor, leading to prolapse of the orbital contents and entrapment of the tissues around the inferior rectus and consequent vertical diplopia.

Adnexal tissue damage

Road traffic accidents, sports injuries and dog bites are common causes of ocular adnexal tissue injury. Eyelid lacerations cause cosmetic and functional problems.

Assessment Perforating globe injury must be ruled out if damage has occurred to these areas. Minor skin lacerations can be closed with Steri-Strips. Damage to the medial side of the lower eyelid can result in damage to the nasolacrimal system. (Repair is difficult with the possibility of chronic watery eye.) Check ocular movements to assess muscle damage and ask for symptoms of diplopia.

Management Full-thickness eyelid lacerations should be repaired by an experienced ophthalmologist, thus if local facilities are inadequate, one should arrange for urgent repatriation. A delay of 48 hours will not necessarily compromise surgical outcome [9]. Irrigate the wounds with sterile balanced salt solution and cover with chloramphenicol ointment and sterile dressings. A tetanus booster and a broad-spectrum antibiotic should be given.

It is worth mentioning that the information here is given as a general guide and clinical scenarios may differ. One should bear in mind that given the opportunity, early assessment by an ophthalmologist or suitably qualified physician is paramount to ensure the best outcome.

Drugs and toxins

Stability of ocular preparations at extremes of temperature and storage

There is surprisingly little information about the stability of ocular preparations at extremes of temperature; however, in general, eye drops should ideally be stored between 2 and 6°C. Almost all preparations are stable up to 25°C. They should be discarded after 1 month unless stated otherwise. It is better to keep them at too cold rather than too hot a temperature, as the active ingredient is likely to remain stable even if the carrier becomes denatured. On return to normal temperature the bottle should be shaken thoroughly, particularly if the preparation is in a suspension, such as dexamethasone.

Ocular toxicity from systemic medication

Chloroquine and hydroxychloroquine

Retinal toxicity does not occur at the recommended dosage when chloroquine is used for malarial prophylaxis. However, visual loss can happen if the patient massively overmedicates with chloroquine when feeling unwell and thinking they have a recurrence of malaria. Hydroxychloroquine is less toxic than chloroquine and is usually used for treatment of rheumatoid arthritis and skin diseases. Treatment is at a much higher dosage than for malaria prophylaxis.

Ethambutol

Ethambutol is used in combination therapy for treating tuberculosis (TB). One per cent of patients on 15 mg/kg develop optic neuropathy, which leads to irreversible visual loss. This is more likely if renal function is poor. Prior to starting ethambutol the following should be documented:

visual acuity, colour vision, pupillary reaction and ophthalmoscopy findings. Patients must be aware of the potential side effects of ethambutol and the need to stop and seek immediate advice should this occur.

Acute closed angle glaucoma induced by drugs likely to be used by a traveller

Elderly and hyperopes are at greater risk of angle closure glaucoma. Most people under the age of 60 are unlikely to develop angle closure unless very hyperopic. Angle closure glaucoma is more common in Orientals and other Asians.

Acute glaucoma is an emergency and treatment needs to be instituted within hours. Laser iridotomies almost always prevent attacks from occurring.

In susceptible people, drugs that cause pupillary dilation can provoke these attacks. Examples are antihistamines. anticholinergics, tricyclic antidepressants and cocaine.

Most preparations carry warnings about the use of a drug, but these refer to closed angle glaucoma rather than primary open angle glaucoma.

Side effects of certain eye medications

Many people do not mention their use of ocular medications. These eye medications could have potentially serious side effects or exacerbate existing health conditions.

Beta-blockers, e.g. Timolol

These drugs may exacerbate asthma and chronic obstructive airways disease, and cause heart block.

Chloramphenicol

Chloramphenicol is cheap and relatively heat stable. Rarely, agranulocytosis has been noted.

Acetazolamide

Acetazolamide is a treatment for glaucoma. It is useful in treating altitude sickness. Patients are rarely on this treatment for long periods of time, as it has quite severe side effects. This includes Stevens–Johnson syndrome, tingling sensation, tiredness, depression, renal stones and renal failure.

Alcohol poisoning and reduction in vision

Travellers may be induced to imbibe some unusual alcoholic drinks when on their journeys. Avoid home-brewed alcoholic beverages, which can contain methanol that is toxic to the optic nerve.

Alcoholics develop vitamin B_{12} deficiency due to poor diet; and smoking of high-tar cigarettes and pipe tobacco can result in optic neuropathy (tobacco-alcohol amblyopia). This is a slow process and reversible in the early stages with hydroxocobalamin injections and a change of habit.

Bee stings

Bee stings around the ocular tissue are common but rarely serious. Removing the sting, a cold compress and antihistamines will help. Cellulitis due to infection can follow a bee sting.

If a corneal sting has occurred, refer to an ophthalmologist for treatment with steroid drops.

Specific infections affecting the eyes in travellers

Travellers may see some of the more esoteric and visually devastating ocular disease when visiting places such as India, Africa and South America. They may become anxious about catching these diseases.

River blindness (onchocerciasis)

This disease is endemic in equatorial Africa and certain areas of Central and South America. Its prevalence is related to the presence of the blackfly. The World Health Organization has made great inroads into its eradication. Travellers are unlikely to become infected unless living in the remote areas.

Trachoma

Trachomal conjunctivitis is seen in close-knit populations living in conditions of poor hygiene and poverty. Up until a few decades ago this existed in the British Isles in places such as in Glasgow and Dublin. Trachoma is encountered in the Middle East, Africa, Indonesia, Central and South America. It has largely been eradicated from India due to effective public health measures. Travellers are unlikely to become infected unless living in endemic areas.

Loa Loa

Infection with this filarial worm is not uncommon in peoples from the equatorial rainforest of Central and West Africa. A biting fly of the genus *Chrysops* transmits the microfilariae. They develop into adult worms in the human host. The thought of harbouring this infestation usually strikes revulsion in the traveller.

Leprosy

Leprosy is found in Africa, Asia and South America. The highest incidence is in Central and West Africa, and among poorer communities in the Indian subcontinent. A quarter of a million leprosy patients are blind. Symptoms take a few years to develop and this depends on the immunity of the patient.

Lyme disease

The ocular manifestations of this tick-borne disease are unusual. This disease is endemic in parts of the US, especially Connecticut, but also in Australia and Asia. In Britain it is seen in the New Forest.

Toxoplasmosis

Humans become infected by this parasite when eating undercooked infected meat and by contamination with cysts following handling of cat litter trays. Serious consequences may arise if a pregnant woman is infected for the first time. Stillbirth can occur in early pregnancy. Retinal scarring can result, but cases can go unrecognised until later in childhood or adult life when there is a reactivation.

Pregnant women should not eat undercooked meat in the UK or abroad, to avoid vertical transmission. In France, steak tartare should be avoided. Barbecued meats should be well grilled or avoided.

Blindness: a global problem

When travelling in the developing world, one is astonished by the number of people with poor vision. Travellers must inevitably wonder why so many people have poor vision and what can be done to prevent or cure blindness.

Seventy-five per cent of those who are blind live in developing countries. As the populations of these countries are both ageing and increasing, the present level of blindness, at 45 million blind globally, is set to increase to 75 million in the next 20 years, given present levels of eye care provision. Eighty per cent of blindness is either preventable or treatable: the challenge is therefore to increase the provision of eye care globally. In light of this, the WHO, the International Agency for the Prevention of Blindness and non-governmental development organisations held meetings to develop a strategy for action to control avoidable blindness. As a result of these meetings, the programme 'Vision 2020: the right to sight' was announced, with the mission statement: 'To eliminate the main causes of blindness in order to give all people of the world, particularly the millions of needlessly blind, the right to sight.' Strategies put forward include widespread use of paramedical workers, a community approach with mobile health workers, and prioritisation and cost analysis. In the first 5 years of a 25-year programme the focus will be on cataract surgery, trachoma, onchoceriasis, childhood blindness and refractive error.

References

1. Epidemiology DEWS Subcommittee (2007) The epidemiology of dry eye disease: report of the epidemiology subcommittee of the International Dry Eye Workshop 2007. *Ocul Surface* **5**(2): 93–106.
2. Wiedman M and Tabin G (1999) High-altitude retinopathy and Altitude Illness. *Ophthalmology* **106**: 1924–1927.
3. Dimmig JW and Tabin G (2003) The ascent of Mount Everest following laser in situ keratomileusis. *J Refract Surg* **19**(1): 48–51.
4. Butler FK (1995) Diving and hyperbaric Ophthalmology. *Surv Ophthalmol* **39**(5): 347–366.
5. Barr C (1983) Prognostic factors in corneoscleral lacerations. *Arch Ophthalmol* **101**: 919–924.
6. Boldt HC *et al.* (1989) Rural endophthalmitis. *Ophthalmology* **96**(12): 1722–1726.
7. Andreoli CM *et al.* (2009) Low rate of endophthalmitis in a large seres of open globe injuries. *Am J Ophthalmol* **147**(4): 601–608.
8. Ross WH and Stockl FA (2000) Visual recovery after retinal detachment. *Curr Opin Ophthalmol* **11**: 191–194.
9. Beadles KA and Lessner AM (1994) Management of traumatic eyelid lacerations. *Semin Ophthalmol* **9**(3): 145–151.

Section VI
Practical issues for travellers

Chapter 24 Travelling with children (including international adoption issues)

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Introduction

The principles guiding the practice of travel medicine are fairly constant regardless of the age of the traveller. The application of these principles, however, varies markedly between children and adults. Children are not merely 'little adults'. Children are unique in regard to size, development, behavioural risks, immune maturity and tolerance of medications. Reviewing available data, this chapter gives practical guidance for medical practitioners providing care to children travelling internationally.

Millions of children cross international borders each year, and lives are frequently enriched from foreign experiences. Clearly, each specific trip carries its own individualised benefits and risks. Every travelling child faces issues of comfort, safety, exposure to germs and readaptation. Pre-travel guidance can help families maximise the benefits of international travel for their children while minimising the health risks. Following travel, personally tailored evaluation and care can also facilitate a healthy entry or re-entry to the ongoing living situation.

In recent years, there has been increased interest in the particular needs of travelling children. Several review articles cover broad areas of paediatric travel medicine [1–9].

Malaria and other insect-borne diseases

Geographical considerations regarding the need for protection from malaria and other insect-borne diseases are similar for children and adults. Within endemic areas, however, the need for protection for children is a critical concern. Children can become very ill very quickly, and they do not always show easily localised signs of infection. Many different illnesses present with fever in children, and even where medical care is good, delayed diagnosis of malaria is common [10, 11]. Children carry the greatest burden of malaria's morbidity and mortality, so careful prevention is necessary for any child spending time in a malaria-endemic area.

No single intervention is 100% protective, and a multifaceted approach to the prevention of insect-borne diseases is needed. Vaccination and chemoprophylaxis are not available for many diseases transmitted by insects, thus the avoidance of bites by mosquitoes and other insects should be a primary focus.

Personal protective measures

Adults travelling with children should be advised particularly to dress children comfortably with clothes exposing minimal amounts of skin and to keep the children in 'mosquito-free zones' during the evening and night hours. Rooms with closed doors and screened windows can keep many of the biting insects away from vulnerable young travellers. Expatriates and others spending prolonged periods in malaria-endemic areas should be advised to avoid leaving stagnant water (a breeding site for mosquitoes) around their dwellings.

Bed nets are available commercially in forms that can fit over a variety of cribs and beds where children might be sleeping. Impregnating bed nets or even curtains with insecticides can also help to protect individuals and has even been shown to decrease morbidity in communities [12–14]. Permethrin-impregnated clothes and pyrethroid-impregnated bed nets are safe for use by children and can offer weeks (clothes) to months (bed nets) of protection after a single impregnation.

N,*N*-diethyl-*meta*-toluamide (DEET) is the 'gold standard' for efficacy as an insect repellent and has been used by hundreds of millions of people of all ages over the past four decades. Newer repellents such as those containing citronella seem to be much less effective [15]. Nonetheless, there has

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been controversy over the safety of DEET-containing insect repellents in children.

Is DEET safe for use in young children? Millions of children use DEET each year, and there have been very few reports of adverse outcomes in children who were using DEET [16]. Some of the unfortunate children with poor outcomes had underlying metabolic abnormalities [17] or applied too much DEET too frequently over unnecessarily extensive body areas [18–20]. Another child with an apparent adverse reaction had apparently licked DEET off her skin and ingested it orally [21]. Details of exposure to DEET are less clear in the other reported cases [22].

More recently, according to the DEET Registry, a post-marketing surveillance system that generates details on medical events temporally associated with DEET use, 296 cases of moderate to major severity were reported from 1995 to 2001 [23]. However, of these cases, only 36 (14.5%) were determined to be probably related and 157 (65%) possibly related to DEET exposure. Approximately 40% of these events occurred in children under 20 years of age, 42% of whom experienced a seizure. No definite relationship between DEET concentration and case severity could be elucidated. The authors concluded that given the extensive use of DEET in the US and the inherent limitations of using passively reported data, the risk of serious adverse events related to the use of DEET repellents is likely minimal [23].

Clearly, DEET has been associated very rarely with tragic outcomes, but there is no clear evidence of causality. In cases where details were available, the exposure seemed to be either oral or over extensive skin surfaces in frequent applications. How should travel medicine practitioners interpret these data? DEET is effective and is safely used by millions of children each year. It spares the inconvenience of insect bites and the risk of insect-borne disease. The use of DEET should be encouraged, but it should be used prudently. It should only be applied on exposed skin, and most of the skin should be covered with clothes. Travel medicine practitioners should remind parents that DEET should not be ingested orally. Thus, special attention should be placed on young children who lick their hands and arms. The concentration of DEET relates to the duration of effective protection but not to the risk of toxicity. Thus, DEET use by children can be encouraged with attention paid to using it only on the few areas of skin that are exposed to insects.

An effective alternative to DEET, picaridin, has been used extensively in Europe and Latin America and is now also recommended for use in the United States by the Centers for Disease Control and Prevention. Picaridin has minimal oral, dermal and inhalation toxicity, and is felt to be safe for children of all ages. Higher concentrations of picaridin (≥19.2%) should be used in areas where life-threatening infections may be transmitted by mosquitoes since formulations of 5–10% provide only around 2 hours of protection. When used in 19.2% concentration, picaridin has been shown to provide similar or better protection than similar concentrations of DEET in both daytime and night-time testing [24].

Personal protective measures are critically important, but they are not universally practised or completely protective. Thus, chemoprophylaxis should be advised for travellers to areas where malaria is endemic. Protective immunity to malaria develops slowly over 2–5 years in children, so prophylactic medications can be necessary for years, despite ongoing exposure to malaria parasites.

Malaria chemoprophylaxis and treatment

The geography of medication resistance by *Plasmodium* parasites is not age-dependent. Nonetheless, the delivery of medication to children differs from that to adults. Dosing details are noted in Table 24.1.

Mefloquine seems to be fully effective and safe in children. Despite past hesitation to use mefloquine in young infants, no significant toxic effects were reported. Its use is now accepted for children of any age. As in adults, mefloquine would not be given routinely to a child with a history of cardiac dysrhythmia or with a known psychiatric disorder. Attention deficit disorder and other behavioural problems have not been associated with mefloquine-induced toxicity. Children with active seizure disorders, however, should not take mefloquine. Since some children with simple febrile

Table 24.1 Malaria chemoprophylaxis in children

Medication	Administration	Dose	Comments
Mefloquine	Weekly	5 mg/kg	Suitable at any age
Doxycycline	Daily	2 mg/kg	Not if <8 years of age
Chloroquine	Weekly	5 mg/kg	Effective in limited geographic areas
Atovaquone/proguanil	Daily	¼ pill per 10 kg max. at 40 kg	250 mg/100 mg adult tablet (or 62.5 mg/25 mg pediatric tablet)
Primaquine (not used routinely)	Daily	0.5 mg/kg	Only if no G6PD deficiency

seizures go on to develop recurrent epileptiform seizures, it is probably best to be judicious about mefloquine use in children less than 6 years old with a history of a previous febrile convulsion. However, since mefloquine is an excellent prophylactic agent in many areas, individualised decisions should be made, weighing the known risk of severe malaria with the unknown but probably small risk of serious mefloquine toxicity in a particular child.

Mefloquine, however, does not taste good, and it is not available in a liquid form. Weekly doses can be weighed and placed by a pharmacist into capsules; capsules can then be opened each week to give the appropriate dose of powdered mefloquine to the child. Alternatively, pills can be cut in quarters with doses rounded off to the nearest quarter pill to be given weekly. Anecdotal reports suggest that the taste of mefloquine is better tolerated when mixed with chocolate or cola-containing soft drinks.

The combination of atovaquone and proguanil has also been studied in children and appears to be safe and effective for children >11 kg [25]. Even though prophylactic dosing of atovaquone/proguanil has not been formally studied in children weighing 5–11 kg, data have been extrapolated to provide dosing recommendations for children in this weight range [26].

Doxycycline is associated with discoloration of developing teeth and might adversely affect the growth of long bones. It is, thus, generally not used in children less than 8 years of age in North America or less than 12 years of age in the UK among other countries.

Chloroquine is safe in children and is effective against the malaria present in a few geographical areas of the world (primarily Central America). Even with long-term weekly use, toxicity has not been noted. Nonetheless, ocular damage has been reported with large doses of chloroquine used over shorter periods of time. Thus, chloroquine use in a child for more than 5 consecutive years should be undertaken only in careful consultation with an ophthalmologist who is following the condition of the child's retinas. As in adults, other rare but reversible adverse effects are possible. Similarly to children using mefloquine, most children do not enjoy the taste of chloroquine, but attempts to 'hide' the taste may help.

The combination of sulfadoxine and pyrimethamine, like other sulfa-containing products, carries about a 1 in 5,000 risk of life-threatening Stevens–Johnson syndrome. Furthermore, unacceptably high rates of treatment failure have been observed when sulfadoxine-pyrimethamine is used to treat malaria [27]. Thus, this combination is not routinely used for prophylaxis in children.

The artemesinin derivatives are short-acting antimalarials developed from a plant originally used in China. For malaria treatment, they are effective only as short-term agents so are not used alone. Artemesinin derivates are not effective as prophylactic agents.

Although not used routinely, there is increasing interest in using primaquine as an agent of causal prophylaxis. As in adults, this product should not be used in children until glucose–6-phosphate dehydrogenase (G6PD) deficiency is ruled out. Recommended dosing is now available for short-term prophylaxis to areas with primarily *P. vivax* malaria [28].

Presumptive treatment is sometimes recommended for adults travelling beyond the reach of accessible medical care. This sort of pre-diagnosis use of malaria treatment is not generally advised for travelling children due to the risk of overtreatment of non-malarial fevers as well as the risk of staying away from medical care when a child has malaria and could deteriorate rapidly.

When malaria treatment is needed in a traveller, the medication selection is the same as in adults. Chloroquine is used orally with a total cure of 25 mg/kg (10 mg/kg once, 5 mg/kg 8 h later, 5 mg/kg 24 and 48 h after the initial dose). Parenteral chloroquine has a narrow therapeutic window and is only used with intensive care unit levels of monitoring. Quinine may be used in a dose of 10 mg/kg three times daily for 7 days. The associated use of tetracyclines for 1 week in treating life-threatening infections is acceptable despite the slight risk of rapid tooth staining. Mefloquine is used either in a 15 mg/kg single treatment dose or in two doses (15 mg/kg first, then 10 mg/kg) separated by 6 h. The artemesinin combination agent co-artemether (containing artemether and lumefantrine) is effective for the treatment of uncomplicated malaria infections in children weighing more than 5 kg, and it is likely to find a useful role in the emergency treatment of febrile pediatric travellers en route to medical care.

Malaria vaccines

With nearly one million children still dying each year due to malaria, an aggressive multinational effort is seeking to develop malaria vaccines [29]. These vaccines would then also presumably be of use to travelling children. Progress is slow, however, since there are multiple forms of the malaria parasite as it goes through its life within humans and since it is not yet clear just what the means are by which children develop anti-malaria immunity.

Nonetheless, there is progress. The RTS,S vaccine includes a recombinant antigen that targets the pre-erythrocytic stage of *P. falciparum*. This vaccine is usually combined with an adjuvant such as AS02A or AS01B. During recent years, the RTS,S/AS02A vaccine has demonstrated effectiveness in laboratory studies of malaria-naive adults, and it also confers some protection in semi-immune adults [30]. This vaccine–adjuvant combination is safe in pre-school and school-aged

children, and it is effective in preventing nearly half of malaria infections and about a third of clinical malaria [31]. The duration of protection following an infant series of three vaccine doses is at least four years [32]. Various vaccine formulations with varying adjuvants, prime-boost techniques and/or concomitant viral vectors continue to be developed [33, 34].

Diarrhoea

Travellers' diarrhoea occurs in children as in adults. The attack rates of diarrhoea for all ages range from 13% to >60% and vary by travel destination [35, 36]. A retrospective survey done in the late 1980s provided age-specific epidemiology of travellers' diarrhoea [37]. The survey involved 363 children who had recently travelled to tropical developing areas of the world after receiving pre-travel advice from an established Swiss travel clinic. Diarrhoea occurred in 40% of travellers aged zero to 2 years, in 9% of children from 3 to 6 years, in 22% of children 7–14 years of age, and in 36% of travellers 15–20 years old. While the numbers of children included in each age group were not large, it seems clear that the incidence of travellers' diarrhoea is similar in children and adults [38] but that the youngest children carry the highest risk. In addition, infants seem to have more severe diarrhoeal illness and had diarrhoea for longer than the other travellers [37]. A more recent retrospective survey that studied a group of 174 Portuguese children who travelled to tropical countries demonstrated a much lower overall incidence of 21.8% [39]. However, as observed in Pitzinger's study, attack rates in younger children were higher.

Aetiology

There is no evidence that the microbiological causes of travellers' diarrhoea differ between adults and children. Studies in adult travellers have found that the aetiology of diarrhoea is similar to that of acute diarrhoea in young children living in less developed countries. The predominant pathogen is enterotoxigenic *Escherichia coli*, followed by varying rates of *Shigella*, *Salmonella* and *Campylobacter* species [40]. Other bacterial causes occur less frequently, as do parasites and viruses. In about a third of cases of travellers' diarrhoea, no pathogenic agent is identified [41].

Prevention

The microbes causing travellers' diarrhoea typically follow oral contamination, presumably due to the ingestion of contaminated food or water. The higher incidence of diarrhoea in young children [37], however, suggests that hand-to-mouth contamination is a likely source of microbes. For children, preventive efforts should include not only food and water hygiene but also handwashing, promotion of clean living spaces, and the avoidance of manual contact with germ-laden materials. Indeed, education about and implementation of hand hygiene measures can markedly decrease the risk of diarrhoeal illness in children [42]. Pacifiers and bottles should be handled only with clean hands as they are prepared for children. Special attention to handwashing around nappy (diaper) changes is also important.

Primum non nocere (first, do no harm) is a fundamental principle guiding medical care. While it would be nice to prevent travellers' diarrhoea pharmacologically in children, potential preventive medications carry significant risks for adverse effects. Bismuth subsalicylate is usually avoided in asymptomatic children due to the association of salicylates with Reye syndrome. Similarly, sulfa-containing antibiotics have been linked occasionally to Stevens–Johnson syndrome, and tetracyclines can stain teeth. Fluoroquinolone antibiotics carry a theoretical risk of damaging growing joints. Although readily used for ill children, these antibiotics are usually avoided in asymptomatic travelling children.

Prevention of travellers' diarrhoea in children is largely based on careful food, water and hand hygiene. Cleanliness is particularly important in young children who frequently put their hands and other objects in their mouths. Aside from hygiene and prudent food and beverage selections, certain probiotics may have some benefit. A recent meta-analysis comparing the efficacy of probiotics for the prevention of travellers' diarrhoea demonstrated that probiotics *Saccharomyces boulardii* and a mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* are efficacious in preventing travellers' diarrhoea [43].

Treatment

Travellers' diarrhoea is usually a self-limited illness, but it does seem to be more severe and more prolonged in young children [37]. Thus, careful attention to prompt treatment is vital.

The mainstay of treatment of diarrhoea in children is oral hydration [44]. Indeed, oral hydration is considered by some to have been the greatest medical advance of the twentieth century. Fluids should be given generously to replace all excessive losses as soon as a child begins to have diarrhoea. Even when mild or moderate dehydration is identified, oral fluids (with appropriate salt and sugar concentrations) are effective [44].

There is controversy over the use of antiperistaltic agents in children. While evidence suggests that one such agent is as effective as oral hydration in travelling young adults [45], there is no evidence that slowing peristalsis actually decreases

fluid losses in young children. In a South African study, an antimotility agent did not change the course of dehydrated children with diarrhoea [46]. Some antimotility medications contain opioids, which, when absorbed, cause sleepiness and altered mental status; they thus make the primary treatment, oral hydration, more difficult. Loperamide is minimally absorbed but is still not generally recommended for or used in young children [47]. A systematic review of loperamide therapy for acute diarrhoea in children found that serious adverse events such as lethargy, ileus or death were reported in 8 out of 927 children who received loperamide, all of whom were less than 3 years old [48]. The authors concluded that adverse events outweigh the benefits of loperamide use in children younger than 3 years. Loperamide is probably both safe and effective when used as an adjunct for the treatment of travellers' diarrhoea in older children and teenagers who are otherwise healthy and with no or minimal dehydration.

Some children with travellers' diarrhoea have significant vomiting. There is emerging evidence in other settings that the use of ondansetron can reduce emesis, intravenous fluid use and hospitalisation in children with acute gastroenteritis [49]. Whether this is effective in young travellers is yet to be determined.

In adult travellers, the decision to initiate presumptive antibiotic therapy is made, in part, based on the social impact of diarrhoea on the traveller's schedule and plans. Children usually have less time-sensitive itineraries, and therapy is often limited to oral hydration for simple (non-dysenteric) travellers' diarrhoea.

When judged necessary, however, travelling children may carry antibiotics to use presumptively in the event of severe travellers' diarrhoea. Of course, diarrhoeal illness with bloody stool or with fever should prompt the family to seek medical attention. In the US, ciprofloxacin (10 mg/kg twice daily) is not generally used for children due to concerns about musculoskeletal toxicity. In fact, this medication seems safe in children [50, 51], but both the benefit and the potential risk would need to be considered in making individual decisions for prepubertal children. Azithromycin has shown good efficacy against the aetiologic agents of travellers' diarrhoea [52] and may be used orally in a dose of 10 mg/kg up to 3 days. Azithromycin is also effective against quinolone-resistant *Campylobacter*, which not infrequently causes childhood travellers' diarrhoea in some areas [53].

Vaccination

While preventive efforts involving behavioural changes and therapeutic medication are often challenging in children, vaccines are well accepted and provide effective pre-travel intervention that can decrease greatly the risk of many diseases. Attention should be paid to the timing of 'routine' childhood vaccines (Table 24.2) as well as to the use of

Table 24.2 'Routine' vaccinations in North America (in accordance with CDC)

Illness/vaccine	'Routine' administration	Acceptable 'early' administration
Hepatitis B	Ages 0–2, 2–4, 6–18 months	2nd and 3rd doses 1 and 4 months after 1st; or, 0, 10 and 21 days with 'booster' at 12 months
Diphtheria	Ages 2, 4, 6, 15 and 60 months, repeat each 10 years	Ages 6, 10 and 14 weeks, 1 and 5 years
Tetanus	Ages 2, 4, 6, 15 and 60 months, repeat each 10 years	Ages 6, 10 and 14 weeks, 1 and 5 years
Pertussis	Ages 2, 4, 6, 15 and 60 months, repeat each 10 years	Ages 6, 10 and 14 weeks, 1 and 5 years
Haemophilus	Ages 2, 4, 6 and 12 months	Ages 6, 10, 14 and 52 weeks
	Only one dose after 12 months	Ages 6, 10,14 and 52 weeks
Pneumococcus	Ages 2, 4, 6 and 12 months. Only one dose after 24 months	
Polio	Ages 2, 4, 6–18 and 60 months	Additional dose at birth
Rotavirus	Ages 2, 4 and 6 months	6 weeks
Hepatitis A	Age 12–23 months	6 months
Measles	Age 12 and 36–60 months	'Extra' dose at 6–9 months 2nd dose 1 month after 1st
Mumps	Age 12 and 36–60 months	Age 12 months
Rubella	Age 12 and 36–60 months	Age 12 months
Varicella	Age 12 and 60 months	Age 12 months
MCV	11–12 years	2 years
HPV	Females 11–12 years	

Table 24.3 Travel-related vaccinations

Illness/vaccine	Usual age	Comments
Hepatitis A	>1 year	6 months
Typhoid, Ty21a, oral	>6 years	
Typhoid, Vi, intramuscular	2 years	
Yellow fever	9 months	Encephalitis risk <4 months of age
Cholera	1 year?	Limited infant data
E. coli	Infancy?	Limited paediatric data
Meningococcus	2 years	A component suitable for 3-month-old infants C component suitable for 2-year-old children
Japanese encephalitis	>l year	12–36-month-old children: ½ adult dose
Rabies	Any age	Underused
Malaria		Pending

special travel-related immunisations (Table 24.3). New vaccines are being developed, and expert recommendations change rapidly. Healthcare providers taking care of travelling children should consult up-to-date national sources (such as www.cdc.gov, www.nathnac.org, www.smartraveller.gov.au and www.who.int) for current recommendations.

'Routine' vaccinations

'Routine' vaccination schedules appropriately vary in different areas due to variations in disease epidemiology and resources. This discussion of 'routine' childhood vaccinations is in accordance with national guidelines of the US.

Diphtheria (D), tetanus (T) and pertussis (P) vaccines are commonly used in most countries of the world. Diphtheria is an unusual illness in many areas but became more common in Europe and Asia following the restructuring of the former Soviet Union, when cases in adult travellers were reported. Tetanus is common around the world, and pertussis continues to cause significant morbidity and mortality in infants. The pertussis vaccine has been plagued by popular concern over side effects, but the acellular vaccines (aP) are effective without as many adverse reactions. The initial series of injections is usually at 2, 4 and 6 months of age in industrialised countries, but it may be given as early as 6, 10 and 14 weeks of age. Travelling infants should be as completely protected as possible before departure. An additional immunisation (DTaP) is given after the first birthday to complete the primary series. A booster of DTaP is given at 4–6 years of age. Older children have waning immunity to pertussis and can serve as reservoirs to pass the microorganisms to younger, at-risk individuals, so revaccination against pertussis is widely recommended for older children and adults. The routine tetanus vaccine booster dose given to children 11–12 years old now incorporates both diphtheria and pertussis vaccines (Tdap). Booster doses of Tdap should be given subsequently every 10 years.

Hepatitis B is common in Africa and Asia, and expatriates even without known body fluid exposure are at risk of this infection [54]. To prevent both acute illness and the risks of later chronic hepatitis and of hepatocellular carcinoma, travellers should consider the full three-dose hepatitis B vaccination course. Administration may begin in the neonatal period, and subsequent doses are given 1–2 months later and then again 6–18 months after the first dose. Accelerated schedules (three doses at 0,10 and 21 days) have been studied and shown to generate a protective response more rapidly than the traditional course (three doses at 0, 1 and 6 months) and to have an equivalent rate of seroprotection after 1 year [55].

Poliomyelitis has been eradicated from the western hemisphere, but cases still occur in Africa and Asia. Travellers to areas that are still endemic should be vaccinated. The oral vaccine is effective but does carry a slight risk of causing vaccine-associated paralytic poliomyelitis. Each dose of either the injectable or the oral vaccine provides some protection, but three doses are usually needed to confer adequate protection against each of the three polio strains. If possible, paediatric travellers should have at least the three initial doses before travelling, doses may be given at 2, 4 and 6 months of age. Younger travellers may receive doses at 6, 10 and 14 weeks of age. A dose at birth is less immunogenic but may be given to children who would not otherwise receive all three initial doses before travelling.

Haemophilus influenzae type b is a major cause of meningitis, pneumonia and other invasive diseases in children around the world. Several good vaccines are available; timing of doses varies with the different products, so package inserts should be consulted. Travelling children under 1 year of age should usually be given three doses of vaccine (usually at 2, 4 and 6 months of age; acceptable at 6, 10 and 14 weeks of age). A single vaccine dose is adequate to provide protection to children over 12 months of age. *H. influenzae* type b disease is very unusual after 5 years of age, so healthy older children do not need this vaccine before travelling if they have not received it previously.

The pneumococcal conjugate vaccine is given to children routinely during infancy. The series is typically given at 2, 4 and 6 months with a booster dose at 12–18 months of

age. A single vaccine dose provides sufficient protection in children over 24 months of age. Pneumococcal conjugate vaccines have been found to be highly efficacious with multiple studies demonstrating a significant decline in invasive pneumococcal disease over the past several years [56]. The impact of this vaccine on pneumonia and otitis media has been less dramatic, but important nonetheless given the high disease burden in young children.

Measles, mumps and rubella are viral illnesses seen around the world. 'Routine' vaccination schedules vary among countries. Passively acquired maternal antibody can impair the effectiveness of these vaccines in young children, but such antibody influences rarely persist beyond the first birthday. Thus, measles vaccine (with or without accompanying mumps and rubella vaccine) may be given after 12 months of age. A second dose is recommended at least 1 month after the first dose to try to provide protection for the small percentage of children who fail to respond to the first dose. Children travelling between 6 and 12 months of age should have an additional dose of measles vaccine before travelling to provide protection in the event that their maternal antibody titres had already waned. Mumps and rubella are particularly problematic illnesses after puberty; unvaccinated travelling children who are nearing puberty should be vaccinated against these illnesses as well.

Varicella vaccine has been available in the US since 1995 and is affordable in many areas of the world. Although varicella illness is less common in some developing countries than in some industrialised regions, varicella vaccine could be given routinely to any immunocompetent paediatric traveller over 1 year of age who has not already had chickenpox. To ensure an adequate immune response, two doses of varicella vaccine are recommended for children 12 months of age and older; they may be given 3 months apart.

Rotavirus is the leading cause of severe gastroenteritis in infants and young children worldwide. Rotavirus vaccine is routinely given in the US at 2, 4 and 6 months of age. The first dose may be given as early as 6 weeks, but must be given by 15 weeks of age. The final dose should be given by 8 months of age.

Hepatitis A is usually asymptomatic in young children and is only rarely associated with life-threatening complications. Nonetheless, children can serve as a reservoir to transmit disease to their older travelling companions or to contacts at home after they return from travel. Hepatitis A vaccines are safe and immunogenic and are now part of the routine immunisation schedule in the US. The vaccine is recommended to be given between 12 and 23 months, with a second dose given 6 months after the first. Limited studies suggest that the vaccine is immunogenic in young children who did not receive hepatitis A antibody passively from their mothers [57, 58]. Thus, even though the vaccine is not usually given before 1 year of age, the offspring of seronegative women can probably receive the vaccine safely and effectively at any age. By 12–15 months of age, titres of passively acquired antibody have usually waned sufficiently to allow adequate vaccine immunogenicity.

Meningococcal vaccines available in the US include a polysaccharide vaccine (MPSV4) and a newer conjugate vaccine (MCV4). Both vaccines are quadrivalent and cover serogroups A, C, Y and W-135. The conjugate vaccine is approved for use in children 9 months of age and older and is routinely recommended for all children between the ages of 11 and 18 years.

Human papilloma virus (HPV) causes approximately 70% of cervical cancer globally. The HPV vaccine was developed to prevent cervical cancer, genital warts and precancerous genital lesions, and is now routinely given to girls 11–12 years of age in some areas and may be used in girls as young as 9 years of age. Vaccination is also recommended for females between the ages of 13 and 26 years old who have not previously been vaccinated. Boys, though not at risk for HPV-related cancers, may be vaccinated to prevent genital warts and to decrease the risk of spread of HPV to future female contacts.

The tuberculosis vaccine, BCG, is used routinely in many countries. This vaccine is of limited and variable efficacy but does seem to reduce disseminated disease in young children. The vaccine may be given at any age. Later, if there is concern about possible tuberculous disease, the history of past BCG vaccination should not affect the interpretation of Mantoux (PPD) skin testing.

Travel-related vaccines

Older children who did not receive the hepatitis A vaccine as part of the routine immunisation protocol should receive it prior to travel. While recommendations often include administration of this vaccine 2 weeks prior to travel, to give time for the development of a protective immune response, the vaccine seems effective even when given after exposure [59]. Thus, vaccine may still be given with confidence up to the time of departure.

Present typhoid vaccines offer better immune protection and fewer side effects than older vaccines. The Vi capsular vaccine is effective in providing some protection for 2 years when given intramuscularly to children 2 years of age and older; it is not adequately immunogenic in younger children. The current Ty21a oral vaccine must be swallowed in capsular form but has documented effectiveness in children. Dosing recommendations vary from three (World Health Organization) to four (American licensing authorities) doses

in the initial series, and the lowest age at which the vaccine is used also varies (2 years by WHO guidelines, 6 years in North America).

Yellow fever vaccine is required for entry into some countries and is recommended for travellers to some other endemic areas. There have been a few cases of vaccine-associated encephalitis, mostly in children under 4 months of age. The vaccine is, therefore, not advised for routine use in children under 9 months of age. Children between 6 and 9 months of age who are at particular risk of exposure to yellow fever might be considered candidates for vaccine use. (Under such circumstances, providers in the US can seek advice from individuals with expertise in yellow fever epidemiology by contacting the Division of Vector-Borne Infectious Diseases or the Division of Global Migration and Quarantine at CDC.) As always, mosquito avoidance measures should also be integrated into the travel plans.

While cholera is not a high-frequency problem in travelling children, the newer oral cholera vaccines do show good efficacy in some parts of the world [60]. As these vaccines become increasingly available on the commercial market, it is expected that they will be useful in children as young as 1 year of age.

Enterotoxigenic *E. coli* (ETEC) is a significant cause of diarrhoea in children less than 3 years old in developing countries. Vaccines against ETEC are being studied, some in association with cholera vaccine. While various ETEC candidate vaccines have demonstrated a protective effect against diarrhoea in adult travellers, the same protective response unfortunately does not appear to occur in infants and young children [61]. Further clinical studies are in progress.

Meningococcal polysaccharide vaccine has limited immunogenicity in young children. The group A vaccine component provides some protection to children as young as 3 months, but the group C component does not induce immune responses reliably before the age of 2 years [62]. As noted earlier, a conjugate meningococcal vaccine is approved for use in children aged 2 years and older, but was found to be poorly immunogenic in infants [63]. A newer quadrivalent glycoconjugate vaccine was recently studied in young infants and found to be immunogenic and well tolerated [64], and is now recommended for travelling children 9 months of age and older.

Japanese encephalitis virus vaccine indications are the same in adults and children. The older mouse-brain derived vaccine is no longer available. A new second-generation inactivated vaccine was recently approved for use in persons 18 years of age or older in the US. In a non-inferiority vaccine trial, this new vaccine was found to have improved efficacy and a better safety profile than the old vaccine [65].

Rabies is still common in much of the world. By their size and location near the ground and by their friendly curiosity for animals, children are particularly at risk. Even long-term expatriates in developing countries, however, often neglect rabies vaccination [66]. When needed, rabies vaccine may be given at any age. As in adults, pre-exposure vaccination does not negate the need for some further care following a subsequent potentially rabid bite. Concurrent use of chloroquine (and, possibly, mefloquine) seems to impede the immune response to rabies vaccine, especially when it is given intradermally. Consequently, rabies vaccination should be completed before prophylactic chloroquine therapy is initiated [67].

Effective malaria vaccines hold the promise of saving the lives of a million children each year in Africa alone. Travellers, too, could be greatly aided by malaria vaccination. DNA vaccines using multiple genetic 'antigens' and unique immunologic boosting techniques are being developed and tested, but are not yet ready or available for general use in travellers.

Comfort

The success and enjoyment of a family's travel often depends on how comfortable their children are. Paediatric travellers are most comfortable when parents view planning and scheduling at least partly from the child's perspective. Travel health practitioners can provide practical suggestions to help families travelling with children.

Long trips can be broken up into smaller segments. Periods of vigorous activity (whether exercise or games) can be mixed with sedate times of transit. Activities can be planned so that the child's mind and body can be occupied. Long waits leading only to 'boring' adult activities can be discouraging to children. Transit nights in hotels with some other activities can help break up trips between several continents.

Age-appropriate activity packs can increase a young child's tolerance of long road and air trips. New snacks, games or books may be opened and used either after a specified duration of travel or when crossing a particular landmark. In this manner, children not only get special new pleasures, but they also mark their advancing progress through the trip.

In aircraft, advanced seat selection can help minimise some of the stress of travelling with children. On intercontinental flights, infants can use fold-out cots attached to walls in front of the bulkhead (front row) seats. Without impeding parental leg room, children can thus stretch out for restful sleep. Families with toddlers should have aisle access for 'walks' around the cabin during long trips. Older children can select air seats with care to obtain a good view of the video screen.

Some families choose to medicate their children to help the child tolerate long periods of inactivity. Sedatives

have not been subject to efficacy studies in paediatric travellers. Diphenhydramine (1 mg/kg per dose) is a commonly used antihistamine drug that provides a few hours of sedation for many children. If a family is going to use it, they should try a test dose before the trip, because some children have a reaction of excitability that can clearly disrupt the trip. Chloral hydrate (50–75 mg/kg per dose) can provide sedation for medical procedures but is not recommended for behavioural control when a child is to be in a confined travel situation. Clearly, parents responsible for supervising travelling children should not personally be under the influence of sedative medications or alcohol.

Typically, the discomfort associated with jet lag seems to increase with age. Nonetheless, children who wake during the night while adjusting to new time zones can disrupt the entire family. Melatonin appears to be safe and has demonstrated efficacy in treating insomnia in children with attention deficit hyperactivity disorder [68], but detailed studies of melatonin for paediatric jet lag have not been done. As noted, sedatives may be given; most experts, however, do not advise that travelling children are given sedatives. Families should plan their schedules and their accommodations in such a way that the disruption of awakening children will be minimised.

Changing cabin pressures in commercial aircraft with ascent and descent have been associated with eustachian tube obstruction and resulting earache in children. This is a particular concern during descent, when 10–15% of young children experience middle ear discomfort [69]. Recommendations for pre-flight use of antihistamines and decongestants have been published, but scientific studies do not demonstrate effectiveness of these products in travelling children. Pseudoephedrine has documented effectiveness in preventing earache in adults [70], but it had no positive effect in a study of young children making commercial air flights [69]. Comfort is also a concern during road trips. Vehicles and car seats should be selected with the child's comfort in mind. The parents' seating location should also be planned to allow supervision and assistance to children without compromising safety.

Motion sickness is a problem for some children. A gentle flow of fresh air and a seat near the front of the vehicle can often help. Dimenhydrinate (1–1.5 mg/kg per dose) is often effective preventive treatment. Scopolamine is also an additional option for children over 12 years of age.

Safety

Accidents and injuries cause more deaths among travellers than do exotic diseases, and injuries are often preventable [71]. Safety should be a major priority of families travelling either domestically or internationally with children.

There is controversy about the seating of infants in aircraft. In general, air travel is safer than road travel, but turbulence and rare crashes do pose risks for incompletely restrained infants in aircraft. Car seats are designed both to restrain general movement and to protect children in accidents where there is a sudden cessation of forward motion. The physical forces caused by air turbulence and plane crashes are much less predictable than the movements of automobile accidents. There is, therefore, no ideally designed infant aircraft restraint seat. Use of car seats in aeroplanes would possibly prevent some injuries and rare deaths. On the other hand, the increased cost of a full airfare for infants using their own restraining seats would prompt some families to use alternative modes of transportation; these other means of transport are actually more likely to be associated with accidents and fatalities. Replacing expensive air trips with long road trips would probably actually increase the risks of infant injury and death. When feasible, families of infants travelling by air might consider using 'car seats' in aeroplanes to decrease further the already low risk of turbulence- and crash-related injury.

Vehicular safety is paramount. Age-appropriate restraints should be available and correctly used for all travellers. Rear-facing car seats are best for children under 12 months of age, and forward-facing restraint seats appropriate for the child's size can be used for older children, even up to 8 years of age. Seat belts should be used by all travellers in cars, and back seats are safer than front seats during accidents. Advance planning is often required to ensure that vehicles of adequate size, with seat belts and car seats, will be available at a particular international destination. Parents of young children are advised to carry their own car seats. Allowing children to move freely about a car endangers the lives of all passengers.

Water-related accidents continue to account for injury and death in children and adolescents. Alcohol should not been consumed during boating. Swimming should always be well supervised with ready help available. Particular attention to boating and propeller safety is necessary [72].

In their homes, most parents are aware of 'child-proofing' and the need to ensure a safe living environment for children. While travelling, care should be paid to electrical outlets, cords and water temperature. Doors, stairs and balconies should be in good repair; a quick inspection at each new lodging site is advisable.

During travel, medicines, cleaning products and chemicals (such as insect repellents) are often exposed and within reach of children. Parents should be especially careful to control a child's environment to decrease the risk of accidental ingestion during trips.

Some injuries occur when young children do not exercise adequate precautions about strangers. Avoiding clothes with visible personal identifiers can help decrease the risk that naive children will allow mal-intentioned adults to identify and 'befriend' them.

Skin safety is also important. Infants under 6 months of age should be shielded from direct sunlight. If sun exposure is unavoidable, a small amount of sunscreen can be used on infants of any age. Preferably, however, infants should be either shaded or have covering clothes to prevent sunburn. Children should use sunscreen with a sun protection factor (SPF) of 15–30, which provides a 93–96% reduction in exposure to ultraviolet B light [73]. Blistering sunburn during childhood is a major risk factor for malignant skin problems later in life.

Travel medicine practitioners should discuss appropriate clothing during pre-travel consultations. Children should wear closed shoes to decrease the risk of helminthic diseases in areas where parasite worms and larvae have contaminated the soil. Clothes and nappies should be ironed before use if they were dried on the ground in an area of tumbu fly infestation.

Despite good parental intentions and efforts, injuries happen and health problems occur. Families should consider travelling with a medical kit to allow prompt response to health problems incurred during their trip. A medical kit could include important health information about the child (name, birth date, weight, medical allergies, immunisation history, doses of current medications and blood type) as well as medicines and supplies. Routine first-aid supplies (bandages, tape, gauze, splints, disinfecting solutions) could be part of a travelling medical kit. Usual medications would be carried, often with two separate supplies in case the traveller is separated from part of the luggage during the trip. Antibacterial skin ointment, steroid creams, antihistamines, analgesics and antipyretics could also be useful. Families should know the size-appropriate dosing for common medications (acetaminophen/paracetamol 10–15 mg/kg per dose every 4 h, ibuprofen 10 mg/kg per dose every 6 h as needed). Medications for travellers' diarrhoea and malaria, when appropriate, could also be included. A family could put oral rehydration fluid packets, sunscreen and insect repellents in their medical kit as well.

Altitude concerns

The Bible teaches that God created humans and placed them in a garden (Genesis 2: 8), probably not far above sea level. There were problems, however, and the original couple were sent travelling (Genesis 3:23–24). Generations later, as the Bible records history, God sent Noah and his family on a high-altitude excursion. Noah's itinerary called for slow ascent *en route* to a high, mountainous elevation (Genesis 7: 17). Travellers since that time have ascended to high altitude more quickly, and acclimatisation challenges are well known.

Children, like adults, are at risk of high-altitude sickness. With the relative immaturity of their cardiovascular systems, however, there are questions about the best management of young children undergoing rapid elevation changes and the resultant exposure to widely varying pressure and oxygen conditions.

Air travel and infants

Anecdotally, there have been sudden, unexplained deaths in infants following long trips in commercial aircraft [74]. This should not be surprising because sudden infant death syndrome (SIDS) is both sudden and idiopathic. Tragically, infants might suddenly die after any coincidental activity, be it air travel, vaccination or kissing. The anecdotal association of a few cases does not prove causality. To date, there is no documented evidence that air travel in pressurised craft increases the risk of sudden death for children. If air travel does increase the risk of SIDS, it is likely to be a less important factor than either prone sleep positioning or passive smoke exposure.

Air travel probably does, however, have physiologic effects on children. Aircraft are pressurised to simulate the atmosphere at an altitude of about 8,000 feet (2,500 m). Under laboratory conditions, some infants had either unusual degrees of hypoxia or increased episodes of abnormal respiratory patterns when subjected to hypoxic ambient air [74]. The clinical implications of these findings, if any, are not known. The data indicate that children respond to conditions simulating high altitude or aircraft exposures, but it is not clear that the responses are either pathologic or dangerous.

Prematurely born infants with chronic lung disease, even if they do not require oxygen at sea level, often show significant oxygen destaturations when exposed to depressurised air simulating aircraft cabins during the first year of life. Consideration for testing or oxygen supplementation would be appropriate for these children prior to air travel [75].

There previously was a published recommendation that children under 6 weeks of age 'should not fly because their alveoli are not completely functional' [76]. This recommendation has been retracted and air travel is now considered safe for all healthy neonates, infants and children. Children with chronic heart or lung disease may be at risk of hypoxia during flight, so should consult with a cardiologist or pulmonologist prior to air travel.

Chronic altitude exposure in infancy

Infants undergo physiologic adaptation when exposed chronically to high altitudes. They initially show decreased oxygen saturations. Over time, they have enhanced oxygen uptake (compared with infants at sea level) with increased ventilation, increased lung compliance and increased pulmonary diffusion. They also have elevations in pulmonary artery pressure and raised blood viscosity [77]. These changes seem useful in providing adequate tissue oxygenation.

In some infants, however, chronic exposure to high altitude has negative effects. Pulmonary hypertension can lead to cardiac decompensation and death [78, 79].

In Tibet, an autopsy study of 15 infants showed pathologic changes suggestive of response to hypoxia [79]. While complete population data were not reported, it was notable that most of the involved infants had been of non-Tibetan origin and had moved to high altitude within a few months of the fatal episode. This suggests that either genetic factors are important or that travellers to high altitude are at greater risk than those who are born at and then stay at altitude.

In Peru, children living at 14,000 feet (4,500 m) elevation were studied. Pulmonary hypertension was common, but this seemed to be less common in older than in younger children [80]. Similarly, a report from Colorado in the US included 11 children with pulmonary hypertension [78]. The nine survivors did well with treatment, relocation to a lower altitude and time.

Putting these reports together, one can conclude that poor outcomes are possible in children developing pulmonary hypertension at high altitude. The exact risk is not quantified, but it appears that immigrants might be at greater risk than those born at altitude. Pending the availability of further data, families should be cautioned about unnecessarily exposing infants to high altitude, and they should be advised to seek medical attention at the earliest sign of any cardiorespiratory symptoms that might develop.

Besides sharing medical risk information, travel health practitioners can help guide the thought processes of parents wondering about taking their children to high altitudes. Clearly, a pleasure trip should not warrant placing the child at much risk at all. A family relocation for humanitarian service or for other less self-gratifying reasons, however, might prompt parents to accept carefully some risk but also to institute contingency plans to respond quickly to any problems that occur.

Altitude sickness

Available information suggests that altitude sickness (be it acute mountain sickness or high-altitude pulmonary oedema) is essentially the same in children and adults. The communication of symptoms will differ with age, but the conditions are similar. Interestingly, high-altitude cerebral oedema does not seem to occur in pre-pubertal children.

In North America's Rocky Mountains, 22% of 3–36-month-old children had symptoms compatible with acute mountain sickness [81]. This is similar to the incidence of acute mountain sickness in adults in that area. Previously, a study had noted that 28% of school-aged children had signs of acute mountain sickness during a vacation at 2,835 m [82]. After rapid ascent to 3,450 m elevation, 38% of children became symptomatic, usually during the first few hours at altitude [83]. Interestingly, however, 21% of a 'control' group vacationing at sea level in that study had similar symptoms. Clearly, other features of travel can mimic acute mountain sickness.

A retrospective review of cases of high-altitude pulmonary oedema suggested that children, but not adults, were more likely to have had an antecedent viral upper respiratory infection when they developed their altitude-related illness [84]. Details of the pathophysiology of this relationship are not known, but families of children with colds might need to be particularly prudent about adjusting high-altitude itineraries and about promptly seeking medical attention (and descending) if tachypnoea develops. Children with trisomy 21 (Down syndrome), especially those with underlying cardiopulmonary disease, also seem to be at increased risk of developing high-altitude pulmonary oedema [85].

Acetazolamide has not been studied systematically for prophylaxis of altitude sickness in children, but is safe when used for other paediatric indications at similar doses. Physiologically, one would expect it to be as effective as in adults, and anecdotal reports suggest nothing to the contrary. It can be used with 2 mg/kg per dose by mouth twice daily beginning 1 day prior to ascent and continuing for the first 3 days at altitude.

In summary, acute complications of ascent to high altitude are similar in children and adults. Minor respiratory symptoms, however, might predispose children to more severe pulmonary complications at altitude.

Body fluid exposures

Adolescents, like adults, may be at risk of sexually transmitted diseases. Through sexual exposure, body piercings, tattooings and non-sterile medical procedures, even children can be exposed to hepatitis B virus, hepatitis C virus and human immunodeficiency virus (HIV). For families travelling together, pre-travel consultation should include reminders of these risks as well as suggestions regarding risk avoidance. For

adolescents travelling with or without their families, confidential discussion of these issues may be necessary.

Post-travel screening and care

The practice of travel medicine goes far beyond pre-travel counsel and care. Indeed, practitioners of paediatric travel medicine are often called on to evaluate returned travellers and recently arrived immigrants. While screening tests and medical care should be individualised to each child's particular situation, some general comments can help focus the care of children who have travelled recently across international borders.

Screening of asymptomatic individuals

Each returned or immigrating traveller carries a wealth of memories and a growing perspective on life. Sometimes, they also carry health concerns and microbial pathogens. Asymptomatic children returning to their home country following a brief overseas trip rarely need to undergo a medical evaluation or screening procedures. Other travellers coming from a prolonged stay in an area of limited hygiene and nutrition deserve extensive screening.

Medical personnel asked to see a child who has immigrated recently or who has returned from a prolonged stay overseas should help facilitate smooth transitions and adjustments to a new or renewed 'home'. While helping the child sense the importance of past experiences, healthcare providers can question the child and parent(s) about cultural, linguistic, scholastic and financial adaptation. Further help can be arranged for a child struggling in any of these areas.

Children settling in to a new geographic area should be incorporated into routine health promotion activities with an identified primary care medical home. The family might benefit from education about routine healthcare and preventive interventions. Vision and hearing screens as well as planned check-ups throughout the school years should be scheduled. Dental problems are common in immigrant children, and dental evaluation is important. Height and weight should be measured, compared with standards for age, and followed over time. Some of these issues are beyond the routine scope of a travel medicine practice, but alert travel medicine practitioners will see that their returned or immigrating travellers are incorporated into these ongoing health maintenance activities.

Immunisation schedules vary around the world. A child should generally be updated with immunisations to be current in the site of the new or ongoing residence. If there is any uncertainty about the reliability of the outside immunisation records, as there often is for adopted children [86], the 'routine' immunisation series should be reinitiated.

Children who have spent more than 3 months in a developing country and children being adopted from situations of uncertain health background can usually benefit from screening procedures. Skin testing for tuberculosis (TB) should be done. Published recommendations help guide the interpretation of results; past receipt of BCG does not exclude the possibility that a positive skin test is due to actual mycobacterial infection [87]. Children with positive test results (greater than 10 mm of induration following a 5 IU intradermal PPD injection) should have chest radiography. If they are asymptomatic without physical findings of tuberculous infection and with a normal chest X-ray, then preventive therapy would be initiated. If they are coming from an area of low incidence of drug-resistant TB, 9 months of isoniazid (10 mg/kg as a daily dose, pyridoxine supplementation if nutritional concerns or other chronic illness) can be given. Children who presumably were exposed to TB in a multidrug-resistant area would use multiple 'preventive' agents. Children with findings of active disease would need further testing and more extensive therapy. A report of extensive TB transmission in an immigrant child highlights the need to place and read TB skin tests in immigrants who seem healthy [88].

Laboratory testing might also be helpful for children who have spent more than 3 months overseas. A blood count with a leukocyte differential reading could give a clue of nutritional anaemia (low haemoglobin concentration with hypochromic, microcytic red blood cells) or of some parasitic diseases (eosinophilia). Hepatitis B testing could help determine if a vaccine course is actually needed (yes, if negative serology) or if further evaluation is indicated (yes, if positive hepatitis B surface antigen) for chronic active hepatitis or for hepatic tumours. HIV serology would be considered for young children who were born to mothers without known medical history, for children who possibly received non-sterile medical intervention or scarification, and for adolescents with sexual contacts. If recent exposure was possible, a repeat HIV serology might be performed 6 months later so as not to miss a child who was seroconverting at the time the first test was done. Syphilis serology could be done if there is concern about an asymptomatic but untreated congenital infection due to unknown maternal condition.

A urinalysis could give a clue to urinary schistosomiasis (haematuria) in an asymptomatic child returning from a long stay in East Africa or another endemic area. Hepatitis C testing is sometimes recommended for foreign-born adoptees [89]. Very young infants and some older children who did not have newborn screening testing might benefit

from screening for conditions such as hypothyroidism, galactosemia, phenylketonuria and haemoglobinopathy.

Stool testing for parasites might uncover silent pre-symptomatic infection, and it might also help prompt early treatment to stop spread to others. For immigrants from areas where specific pathogens are known to be common, presumptive treatment with an agent such as albendazole is recommended [90]. For individual returned travellers who spent months around areas of poor hygiene, microscopic testing of stool is advised. Repeating examinations on three different days increases the yield of positive findings. Young children who have been exposed to non-toilet-trained peers could benefit from specific *Giardia* antigen testing, as these parasites are sometimes missed on stool microscopy. Bacterial stool culture is rarely needed in asymptomatic returned travellers.

Screening tests should be done if they are feasible practically and if a positive finding could result in an intervention that would benefit either the child or the child's contacts. Each returned or immigrating traveller comes with specific risks based on their itinerary, age, medical condition and exposures. Table 24.4, however, gives some general guidelines that might help a travel medicine practitioner decide on screening tests. Further perspectives on screening of newly arrived, internationally travelling children are also available in the medical literature [86, 89, 91–94].

Table 24.4 Screening of asymptomatic returned or immigrating travellers

If brief international trip:
No tests
If more than 3 months in a developing country:
Growth parameters
Developmental screening
Psychosocial, scholastic and cultural adjustment
TB skin test
Complete blood count
Stool microscopy for parasites (also *Giardia* antigen if young)
If cutaneous exposure to fresh water in an area with schistosomiasis:
Urinalysis (for haematuria)
Stool microscopy
Possibly, schistosomal serology
If risky sexual contact or if received medical care, scarification or piercings of uncertain sterility:
HIV serology
Hepatitis B serology
Hepatitis C serology
If foreign born, less than 6 months of age, and/or uncertain maternal health history:
'Routine' newborn screening (phenylketonuria, hypothyroidism, galactosemia, haemoglobinopathy, perhaps others)
Syphilis serology

Caring for symptomatic travellers and immigrants

Children found to have abnormalities on history, physical examination or initial screening tests should obviously undergo further evaluation and care. The evaluating health-care provider should be cognizant of important 'foreign diseases'. The evaluation and care of ill paediatric travellers has been reviewed [95].

Fever is a common symptom in children, but the presence of fever in any child who has been in a malaria-endemic area in recent months should prompt emergent consideration of malaria as a cause of fever. As mentioned, malaria is often a delayed diagnosis in a non-endemic region [10, 11, 96]. Anaemia, thrombocytopenia and hepatosplenomegaly should prompt ongoing concern for malaria even if the initial malaria smear is negative. Tachypnoea is an important finding of severe malaria that can predict a poor outcome; this finding should not be overlooked [97]. The laboratory evaluation and medical management of malaria is similar in children as in adults. Doses of antimalarials would be adjusted on the basis of body weight, and tetracyclines are used only if necessary for life-threatening infection in children under 8 years old. Fever could also be due to rickettsial disease or typhoid fever.

Diarrhoea persisting for more than 2 weeks should also prompt a search for the aetiologic agent. A foul odour with non-bloody but greasy-looking stool and excessive flatulence suggests a diagnosis of giardiasis. Bloody stool in a febrile child suggests a bacterial aetiology such as shigellosis. Bloody stool in an afebrile child could represent amoebiasis.

Organising the care of paediatric travellers

Many general physicians are neither comfortable nor competent in caring for international travellers. Some travel medicine specialists are not fully at ease in seeing travelling children. How, then, should paediatric travel medicine services be organised?

One academic centre in the US reported on its experience in caring exclusively for paediatric travellers [98]. Children came after referral from other physicians, but their adult travelling companions were required to obtain pre-travel care elsewhere.

Another model is to provide 'full service' pre-travel care to travellers of all ages. A recent report describes the combined effort of an academic centre and a governmental health department [99]. At one setting and at the same time, physicians trained in both paediatrics and travel medicine provided counsel to all members of families and groups travelling with children. Individuals travelling without children were scheduled preferentially to see a different travel medicine specialist who did not have particular paediatric expertise.

Children travelling overseas to visit friends and relatives are at great risk of adverse outcomes [100]. In an urban American setting, a travel health service based in a hospital focused on providing care to these children [101].

Usually, travel medicine specialists provide care for travellers of all ages. They must merely be comfortable with their own limitations and know when to seek outside input on specific patients, be they paediatric, immunocompromised or otherwise unique.

Training the next generation

International organisations such as the International Society of Travel Medicine and the American Society of Tropical Medicine and Hygiene have taken a lead in the training and certification of travel medicine specialists. Meanwhile, individual travel medicine practitioners are mentoring the next generation of specialists. International experience by trainees is beneficial in shaping future career interests and styles [102], and guidelines for the implementation of useful overseas rotations for paediatric trainees are available [103, 104].

Conclusion

Karl Neumann, a senior authority in the field of paediatric travel medicine, wrote: 'Children make great travellers. They are inquisitive, fun, and when they choose, inexhaustible. Taking children on trips exposes them to new experiences, sows family togetherness, and builds memories for tomorrow.' [105] This is already true, yet this is also still the goal. Caring for children who travel internationally is a great privilege. As we work to prevent and treat travel-related injury and illness, we can help families maximise the benefits of their international experiences. Together, we can help build favourable memories that will live on through the next generation.

References

1. Sohail MR and Fischer PR (2005) Health risks to air travellers. *Infect Dis Clin N Am* **19**: 67–84.
2. Summer AP and Fischer PR (2005) Travel with infants and children. *Clin Fam Pract* **7**: 729–743.
3. Leggat PA and Fischer PR (2006) Accidents and repatriation. *Travel Med Infect Dis* **4**: 135–146.
4. Hill DR *et al.* (2006) The practice of travel medicine: guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* **43**: 1499–1539.
5. McGovern LM *et al.* (2007) Congenital infections associated with international travel during pregnancy. *J Travel Med* **14**: 117–128.
6. Stauffer W *et al.* (2008) Preparing children for international travel. *Travel Med Infect Dis* **6**: 101–113.
7. Greenwood CS *et al.* (2008) Immunization issues in pediatric travellers. *Expert Rev Vaccines* **7**: 651–661.
8. Christenson JC (2008) Preparing families with children travelling to developing countries. *Pediatr Ann* **37**: 806–813.
9. Rosenman JR and Fischer PR (2011) Travel clinics – what are they? *Pediatr Ann* **40**: 371–375.
10. Emanuel B *et al.* (1993) Malaria in children in Chicago. *Pediatrics* **92**: 83–85.
11. Viani RM and Bromberg K (1999) Pediatric imported malaria in New York: delayed diagnosis. *Clin Pediatr* **38**: 333–337.
12. D'Alessandro U *et al.* (1995) Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme. *Lancet* **345**: 479–483.
13. Habluetzel A *et al.* (1999) Insecticide-treated curtains reduce the prevalence and intensity of malaria infection in Burkina Faso. *Trop Med Int Health* **4**: 557–564.
14. Lengeler C (2004) Insecticide-treated bednets and curtains for preventing malaria. *Cochrane Database Systematic Reviews* (**2**): CD000363.
15. Fradin MS (1998) Mosquitoes and mosquito repellents: a clinician's guide. *Ann Intern Med* **128**: 931–940.
16. Fischer PR and Christenson JC (1998) Concentrated DEET safe-and sometimes necessary (letter). *Contemp Pediatr* **15**: 25–28–204.
17. Heick HMC *et al.* (1980) Reye-like syndrome associated with use of insect repellent in a presumed heterozygote for ornithine carbamoyl transferase deficiency. *J Pediatr* **97**: 471–473.
18. Roland EH *et al.* (1985) Toxic encephalopathy in a child after brief exposure to insect repellents. *Can Med Assoc J* **132**: 155–156.
19. Lipscomb JW *et al.* (1992) Seizure following brief exposure to the insect repellent *N,N*-diethyl-*m*-toluamide. *Ann Emerg Med* **21**: 315–317.
20. Zadikoff CM (1979) Toxic encephalopathy associated with use of insect repellent. *J Pediatr* **95**: 140–142.
21. Edwards DL and Johnson CE (1987) Insect-repellent-induced toxic encephalopathy in a child. *Clin Pharm* **6**: 496–498.
22. Osimitz TG and Murphy JV (1997) Neurological effects associated with use of the insect repellent *N,N*-diethyl-*m*-toluamide (DEET). *Clin Toxicol* **35**: 435–441.
23. Osimitz TG *et al.* (2010) Adverse events associated with the use of insect repellents containing N,N-diethyl-m-toluamide (DEET). *Regul Toxicol Pharm* **56**: 93–99 .
24. Frances SP *et al.* (2002) Field evaluation of repellent formulations against daytime and nighttime biting mosquitoes in tropical rainforest in northern Australia. *J Med Entomol* **39**: 541–544.

25. Lell B *et al.* (1998) Randomized placebo-controlled study of atovaquone plus proguanil for malaria prophylaxis in children. *Lancet* **351**: 709–713.
26. Boggild AK *et al.* (2007) Atovaquone-proguanil: report from the CDC expert meeting on malaria chemoprophylaxis (ii). *Am J Trop Med Hyg* **76**: 208–223.
27. Eriksen J *et al.* (2008) Antimalarial resistance and DHFR/DHPS genotypes of Plasmodium falciparum three years after introduction of sulfadoxine-pyrimethamine and amodiaquine in rural Tanzania. *Trans Roy Soc Trop Med Hyg* **102**: 137–142.
28. Centers for Disease Control and Prevention (CDC) (2009) *Health Information for International Travel 2010*. US Department of Health and Human Services, Public Health Service, Atlanta.
29. Breman JG and Plowe CV (2009) A malaria vaccine for control: more progress. *J Infect Dis* **200**: 317–320.
30. Kester KE *et al.* (2009) Randomized, double-blind, phase 2a trial of falciparum malaria vaccines RTS,S/AS01B and TRS,S/AS02A in malaria-naïve adults: safety, efficacy, and immunologic associates of protection. *J Infect Dis* **200**: 337–346.
31. Abdulla S *et al.* (2008) Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. *New Engl J Med* **359**: 2533–2544.
32. Sacarlal J *et al.* (2009) Long-term safety and efficacy of the RTS,S/AS02A malaria vaccine in Mozambican children. *J Infect Dis* **200**: 329–336.
33. Dunachie SJ *et al.* (2006) A DNA prime-modified vaccinia virus Ankara boost vaccine encoding thrombospondin-related adhesion protein but not circumsporozoite protein partially protects healthy malaria-naïve adults against Plasmodium falciparum sporozoite challenge. *Infect Immun* **74**: 5933–5942.
34. Draper SJ *et al.* (2008) Effective induction of high-titer antibodies by viral vector vaccines. *Nature Med* **14**: 819–821.
35. Calvacanti A *et al.* (2002) Traveler's diarrhea: epidemiology and impact on visitors to Fortaleza, Brazil. *Revista Panamericana de Salud Publica* **11**: 245–252.
36. Steffen R (2005) Epidemiology of traveler's diarrhea. *Clin Infect Dis* **41**(Suppl. 8): S536–S540.
37. Pitzinger B *et al.* (1991) Incidence and clinical features of traveler's diarrhea in infants and children. *Pediatr Infect Dis J* **10**: 719–723.
38. Steffen R *et al.* (1999) Epidemiology, etiology, and impact of traveler's diarrhea in Jamaica. *JAMA: J Am Med Assoc* **281**: 811–817.
39. Silva FG *et al.* (2009) Travelers' diarrhea in children visiting tropical countries. *J Travel Med* **16**: 53–54.
40. Paredes P *et al.* (2000) Etiology of travelers' diarrhea on a Caribbean Island. *J Travel Med* **7**: 15–18.
41. Peltola H and Gorbach S (1997) Travelers' diarrhea: epidemiology and clinical aspects. In: DuPont HL and Steffen R (eds) *Textbook of Travel Medicine and Health*, pp. 78–86. Decker, Hamilton, Ontario.
42. McDonald E *et al.* (2008) Are hygiene and public health interventions likely to improve outcomes for Australian Aboriginal children living in remote communities? A systematic review of the literature. *BMC Public Health* **8**: 153.
43. McFarland LV (2007) Meta-analysis of probiotics for the prevention of traveler's diarrhea. *Travel Med Infect Dis* **5**: 97–105.
44. American Academy of Pediatrics (1996) Practice parameter: the management of acute gastroenteritis in young children. *Pediatrics* **97**: 424–436.
45. Caeiro JP *et al.* (1999) Oral rehydration therapy plus loperamide versus loperamide alone in the treatment of traveler's diarrhea. *Clin Infect Dis* **28**: 1286–1289.
46. Bowie MD *et al.* (1995) Loperamide for treatment of acute diarrhoea in infants and young children. A double-blind placebo-controlled trial. *S Afr Med J* **85**: 885–887.
47. Gattuso JM and Kamm MA (1994) Adverse effects of drugs used in the management of constipation and diarrhea. *Drug Safety* **10**: 47–65.
48. Su-Ting T *et al.* (2007) Loperamide therapy for acute diarrhea in children: systematic review and meta-analysis. *Plos Med* **4**: 495–505.
49. DeCamp LR *et al.* (2008) Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. *Arch Pediat Adol Med* **162**: 858–865.
50. Schaad UB *et al.* (1995) Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. *Pediatr Infect Dis J* **14**: 1–9.
51. Jick S (1997) Ciprofloxacin safety in a pediatric population. *Pediatr Infect Dis J* **16**: 130–134.
52. Khan WA *et al.* (1997) Treatment of shigellosis: comparison of azithromycin and ciprofloxacin. *Ann Int Med* **126**: 697–703.
53. Cabada MM and White AC (2008) Travelers' diarrhea: an update on susceptibility, prevention, and treatment. *Curr Gastroenterol Rep* **10**: 473–479.
54. Lange WR and Frame JD (1990) High incidence of viral hepatitis among American missionaries in Africa. *Am J Trop Med Hyg* **43**: 527–533.
55. Bosnak M *et al.* (2002) Accelerated hepatitis B vaccination schedule in childhood. *Pediatr Int* **44**: 663–665.
56. Pavia M *et al.* (2009) Efficacy of pneumococcal vaccination in children younger than 24 months: a meta-analysis. *Pediatrics* **123**: e1103–e1110.
57. Troisi CL *et al.* (1997) Immunization of seronegative infants with hepatitis A vaccine (Havrix; SKB): a comparative study of two dosing schedules. *Vaccine* **15**: 1613–1617.
58. Piazza M *et al.* (1999) Safety and immunogenicity of hepatitis A vaccine in infants: a candidate for inclusion in the childhood vaccination programme. *Vaccine* **17**: 585–588.
59. Sagliocca L *et al.* (1999) Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomised trial. *Lancet* **353**: 1136–1139.
60. Mahalanabis D *et al.* (2008) A randomized, placebo-controlled trial of the bivalent killed, whole-cell, oral cholera vaccine in adults and children in a cholera endemic area in Kolkata, India. *PLoS ONE* **3**: e2323.
61. Svennerholm AM and Tobias J (2008) Vaccines against enterotoxicgenic *Escherichia coli*. *Exp Rev Vaccines* **7**: 795–804.
62. American Academy of Pediatrics (2009) Meningococcal infections. In: Pickering LK *et al.* (eds) *Red Book 2009: Report of the Committee on Infectious Diseases*, 28th edn, pp. 461, 681–685. American Academy of Pediatrics, Elk Grove Village, Illinois.
63. Rennels M *et al.* (2004) Dosage escalation, safety, and immunogenicity study of four dosages of a tetravalent meningococcal

polysaccharide diphtheria toxoid conjugate vaccine in infants. *Pediatr Infect Dis J* **23**: 429–435.
64. Perrett KP *et al.* (2009) Immunogenicity and immune memory of a nonadjuvanted quadrivalent meningococcal glycoconjugate vaccine in infants. *Pediatr Infect Dis J* **28**: 186–193.
65. Tauber E *et al.* (2007) Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. *Lancet* **370**: 1847–1853.
66. Arguin PM *et al.* (2000) Survey of rabies preexposure and postexposure prophylaxis among missionary personnel stationed outside the United States. *J Travel Med* **7**: 10–14.
67. Taylor DN *et al.* (1984) Chloroquine prophylaxis associated with a poor antibody response to human diploid cell rabies vaccine. *Lancet* **1**: 1405.
68. Van der Heijden KB *et al.* (2007) Effect of melatonin on sleep, behaviour, and cognition in ADHD and chronic sleep-onset insomnia. *J Am Acad Child Adol Psych* **46**: 233–241.
69. Buchanan BJ *et al.* (1999) Pseudoephedrine and air travel-associated ear pain in children. *Arch Pediat Adol Med* **153**: 466–468.
70. Csortan E *et al.* (1994) Efficacy of pseudoephedrine for the prevention of barotrauma during air travel. *Ann Emerg Med* **23**: 1324–1327.
71. Reid D and Keystone JS (1997) Health risks abroad: general considerations. In: DuPont HL and Steffen R (eds)*Textbook of Travel Medicine and Health*, pp. 3–9. Decker, Hamilton, Ontario.
72. Fischer PR (1998) Summer, travel, and injuries. *Travel Med Advisor* **8**: 25–26.
73. Kim HJ *et al.* (1997) Here comes the sun. *Contemp Pediatr* **14**: 41–69.
74. Parkins KJ *et al.* (1998) Effect of exposure to 15% oxygen on breathing patterns and oxygen saturation in infants: interventional study. *Br Med J* **316**: 887–894.
75. Udomittipong K *et al.* (2006) Pre-flight testing of preterm infants with neonatal lung disease: a retrospective review. *Thorax* **61**: 343–347.
76. Centers for Disease Control and Prevention (1999) *Health Information for International Travel 1999–2000*. US Department of Health and Human Services, Atlanta, p. 212.
77. De Meer K *et al.* (1995) Physical adaptation of children to life at high altitude. *Eur J Pediatr* **154**: 263–272.
78. Khoury GH and Hawes CR (1963) Primary pulmonary hypertension in children living at high altitude. *J Pediatr* **62**: 177–185.
79. Sui GJ *et al.* (1988) Subacute infantile mountain sickness. *J Pathol* **155**: 161–170.
80. Sime F *et al.* (1963) Pulmonary hypertension in children born and living at high altitudes. *Am J Cardiol* **11**: 143–149.
81. Yaron M *et al.* (1998) The diagnosis of acute mountain sickness in preverbal children. *Arch Pediat Adol Med* **152**: 683–687.
82. Theis MK *et al.* (1993) Acute mountain sickness in children at 2835 meters. *Am J Dis Child* **147**: 143–145.
83. Bloch J *et al.* (2009) Prevalence and time course of acute mountain sickness in older children and adolescents after rapid ascent to 3450 meters. *Pediatrics* **123**: 1–5.
84. Durmowicz AG *et al.* (1997) Inflammatory processes may predispose children to high-altitude pulmonary edema. *J Pediatr* **130**: 838–840.
85. Durmowicz AG (2001) Pulmonary edema in 6 children with Down syndrome during travel to moderate altitudes. *Pediatrics* **108**: 443–447.
86. Hill DR (1998) The health of internationally adopted children. *Travel Med Advisor Update* **8**: 17–20.
87. American Academy of Pediatrics (2009) Tuberculosis. In: Pickering LK *et al.* (eds) *Red Book 2009: Report of the Committee on Infectious Diseases*, 28th edn, pp. 681–685. American Academy of Pediatrics, Elk Grove Village, Illinois.
88. Curtis AB *et al.* (1999) Extensive transmission of *Mycobacterium tuberculosis* from a child. *New Engl J Med* **341**: 1491–1495.
89. Miller LC (1999) Caring for internationally adopted children. *New Engl J Med* **341**: 1539–1540.
90. Muennig P *et al.* (1999) The cost effectiveness of strategies for the treatment of intestinal parasites in immigrants. *New Engl J Med* **340**: 773–779.
91. Hayam KC and Pickering LK (1991) Screening of immigrant children for infectious diseases. *Adv Pediatr Infect Dis* **6**: 91–110.
92. Stevens GW and Vollebergh WA (2008) Mental health in migrant children. *J Child Psychol Psyc* **49**: 276–294.
93. Mandalakas AM and Starke JR (2004) Tuberculosis screening in immigrant children. *Pediatr Infect Dis J* **23**: 71–72.
94. Stauffer WM (2002) Screening of international immigrants, refugees, and adoptees. *Primary Care* **29**: 879–905.
95. Fischer PR (1998) Pediatric problems during and after international travel. In: Bia F (ed.) *Travel Medicine Advisor*, pp. TC2.9–TC2.18. American Health Consultants, Atlanta, Georgia.
96. Centers for Disease Control and Prevention (2006) Malaria in multiple family members – Chicago, Illinois, 2006. *MMWR. Morbid Mortal Wkly Rep* **55**: 645–648.
97. Marsh K *et al.* (1995) Indicators of life-threatening malaria in African children. *New Engl J Med* **332**: 1399–1404.
98. Walter EB and Clements DA (1998) Travel consultation for children in a university-affiliated primary care setting. *Pediatr Infect Dis J* **17**: 841–843.
99. Christenson JC *et al.* (2000) Pediatric travel consultation in an integrated clinic. *J Travel Med* **8**: 1–5.
100. Bacaner N *et al.* (2004) Travel medicine considerations for North American immigrants visiting friends and relatives. *JAMA: J Am Med Assoc* **291**: 2856–2864.
101. Hagmann S *et al.* (2009) Travel health care for immigrant children visiting friends and relatives abroad: retrospective analysis of a hospital-based travel health service in a US urban underserved area. *J Travel Med* **16**: 407–412.
102. Gupta AR *et al.* (1999) The international health program: the fifteen-year experience with Yale University's internal medicine residency program. *Am J Trop Med Hyg* **61**: 1019–1023.
103. Torjesen K *et al.* (1999) International child health electives for pediatric residents. *Arch Pediat Adol Med* **153**: 1297–1302.
104. Suchdev P *et al.* (2007) A model for sustainable short-term international medical trips. *Ambulatory Pediatr* **7**: 317–320.
105. Neumann K (1995) Traveling with infants and young children. *Pediatr Basics* **73**: 12–20.

Chapter 25 Women's health and travel

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Introduction

Travel health issues for individual women will vary according to their life stage and lifestyle. Considerations will differ, for instance, between a woman in her second trimester of pregnancy and about to work in a refugee camp, and an 80-year old grandmother about to go on her first trip around the world.

In this chapter we will attempt to outline the various issues that need to be addressed regarding travel at the different stages in a woman's life cycle, including pregnancy, and identify steps to protect her health and safety. We will also point out areas in which some diseases cause effects that are specific to women.

Pre-travel assessment

Table 25.1 outlines a suggested pre-travel assessment for women travellers.

Menstruation

The changes in time zones, diet, exercise and sleep patterns that occur with travel can affect the woman's hypothalamic-pituitary axis and cause alterations in the menstrual cycle and premenstrual symptoms. Instructions need to be given regarding amenorrhoea or abnormal uterine bleeding [1]. The patient should also be advised to bring adequate supplies of feminine hygiene products as these might not be available. Disposal of these products should also be considered, or perhaps their replacement with such items as a soft, reusable rubber cup. Medications for self-treatment of premenstrual symptoms should be included in the medical kit even for women who may not normally experience such symptoms (*see* Table 25.2).

Some women prefer not to have a menstrual period while travelling. They may then take oral contraceptives without a pill-free interval, but should be warned that a small amount of breakthrough bleeding may occur [2, 3].

Sexually active women may wish to carry pregnancy tests as these are not always available or reliable at some destinations. Such kits would be helpful in the evaluation of amenorrhoea or if there is suspicion of an ectopic pregnancy. They should have an adequate shelf life and be protected from environmental extremes.

Urinary tract issues

Dehydration, lack of convenient toilets or hygiene, or an increase in sexual activity may all result in urinary tract infection. Measures to prevent this include a brisk fluid intake and urinating wherever there is access to a toilet. An appropriate choice of attire may facilitate squatting when necessary, and if needed there are funnels designed to assist women to urinate in the standing position. The traveller should also carry a supply of toilet paper or pre-moistened towelettes. Patients should be taught the symptoms of a urinary tract infection and be provided with oral antibiotics and a urinary analgesic agent.

Some women suffer from urinary incontinence and older women may also experience vaginal dryness and urinary symptoms. An appropriate specialist may advise pelvic floor exercises, panty liners or medications such as oestrogen vaginal cream, vaginal rings or an oral contraceptive pill inserted vaginally [4–6].

Vaginal discharge and itching

Changes in a woman's bacterial flora may result in vaginal discharge or itching. One of the common causes is yeast vaginitis, manifested by a thick, white discharge and usually

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Table 25.1 Pre-travel checklist for women travelers

Pre-travel consultation for women travellers should take into account the individual life stage and the lifestyle of a woman:

- Itinerary
- Age
- Immunisation history – need for updates
- Reproductive issues
  - Menstruation
  - Contraceptive need
  - Contraceptive choice
  - Emergency contraception
  - Pregnancy
    - Planned
    - Unplanned
  - Lactation
  - Perimenopausal and menopausal issues
  - Sexually transmitted disease risk
    - Partners: men, women or both
    - Preventative measures/treatment
    - HIV post exposure prophylaxis
- Medical issues
  - Urinary tract
  - Vaginitis
- Other significant past medical history
- Long-term travel-need baseline data
  - Pap smear
  - Mammogram
  - Carry copy of electrocardiogram if over 50
  - Psychological issues
    - Loneliness
    - Depression
    - Isolation
  - Gender-specific recommendations related to disease exposure according to itinerary
  - Gender-specific recommendations related to sports/environment
  - Altitude
  - Scuba
- Cultural issues
- Personal safety
- Travel medicine kit
- Emergency plans
  - Carry copy of medical record
  - Emergency resources – medical and evacuation insurance
  - Website
  - Mobile phone access

severe itching. It is more likely when antibiotics are used. Several creams and suppositories are available or some women prefer to use an oral treatment such as fluconazole. She might also use a mild hydrocortisone cream for the itching.

The discharge of a bacterial vaginosis is usually more of a greyish colour and has a fishy odour. Treatment is metronidazole or clindamycin vaginal cream or tablets.

The patient should be advised to seek medical evaluation if the symptoms do not improve with self-treatment. Discharge or pelvic pain following a new sexual encounter may represent a sexually transmitted disease and should be evaluated.

Sexually transmitted diseases

Safe sex practices and the risks of sexually transmitted diseases should be included as part of the pre-travel visit [7]. Complications include pelvic inflammatory disease, chronic pelvic pain and infertility.

Women should avoid casual sex and always use condoms, no matter what other means of contraception are being used. A male or female condom made of polyurethane is an effective alternative for persons allergic to latex.

HIV prophylaxis

Women should be educated about the availability of post-exposure HIV prophylaxis for high-risk sexual exposures or sexual assault. If travel is to a remote area, the initial 2 weeks of treatment should be included in the traveller's medical kit. Providers may check with the Centers for Communicable Disease (CDC) or similar source for the latest recommendations [8, 9].

Contraception

Advice to all travellers of reproductive age should include recommendations on contraceptive use. Emergency contraception options should also be reviewed. This is a rapidly changing field and options around the world vary [10, 11].

If a woman is already using a contraceptive method, it should be evaluated for ease of use, reliability and any changes required due to travel. A new method should be used for several months prior to travel, especially in the case of a long-term assignment or travel to a remote area. Back-up methods should be discussed.

Common methods are reviewed in Table 25.3. Considerations include length of travel, ease of use, possible environmental effects and accessibility.

Women on oral contraceptives should be advised to take adequate supplies as the same formulation may not be available elsewhere. An empty package may be helpful in finding an alternative. Although an alternative formulation may be effective in preventing pregnancy it may result in more side effects than the formulation usually taken.

Table 25.2 Woman's pre-travel checklist

Problem	Patient teaching	Necessary supplies	Medications
Menstruation		Pads, tampons, menstrual cups Paper towelettes/plastic disposal bags Calendar to keep track of menses	
Premenstrual syndrome		PMS medication	NSAIDs Unclear benefit, studies underway – quai, ginseng, black cohash, vitex/chasteberry, melatonin, St John's wort, wild yams (contain diosgenin, the starting point for the synthesis for progestins; human body does not have enzyme to convert progesterone from yams)
Urinary infections	Urinary tract infections Pyelonephritis – if fever, nausea and flank pain suspect upper tract disease	Optional screening test for UTI Toilet tissue, towelettes Funnels – paper or plastic Mild soaps Urinary dipstick to check for leukocytes and nitrites Leukocyte esterase strips	Urinary antibiotic Urinary analgesic. Pyridium 200 mg t.i.d. for dysuria
Vaginitis	Bacterial vaginosis	Self-diagnosis tool for BV pH paper: Ph > 4.7	Vaginal creams for BV Metrogel, clindamycin Oral antibiotics for BV Metronidazole, clindamycin
	Vaginitis – candidiasis	Loose airy clothes Self-diagnosis tool pH paper: pH < 4.5 acidophilic	Vaginal creams – Candida. Monistat vaginal cream Nystatin Vaginal suppositories Oral medication for candidiasis. Fluconazole 150 mg × 1
	Pruritus		Hydrocortisone cream for pruritus
Contraception	New method of contraception to be used Carry extras, depending on length of trip Review options in country of destination	Pregnancy tests Chart – to keep track of pills if using them, menstrual periods Timer-special wrist watch 'alarm' to use for oral contraceptive pill dosing when changing time zones, travelling Male/female condoms Diaphragm/cap/sponge Spermicides – contraceptive creams, jellies, films	Combined pill regimen or levonorgestrel regimen
Emergency contraception		Preventative barrier measures – condoms, dental dams, saran wrap, gloves, barrier methods	Misoprostol (RU-486) China, some European countries, US
Sexually transmitted infections	Trichomoniasis	Magnifying glass	Metronidazole

(*Continued*)

Table 25.2 (*Continued*)

Problem	Patient teaching	Necessary supplies	Medications
		STD chart – for identifying basics – recommendations for treatment	Medicine for treatment – azithromycin, cipro/orofloxin, aciclovir/famciclovir Emergency post-exposure HIV prophylaxis for high-risk unprotected sexual encounter Zidovudine 200 mg t.i.d. for 4 weeks Lamivudme 150 mg b.i.d. for 4 weeks. Add indmavir 800 mg t.i.d./nehnavir for high-risk exposure or if zidovudine-resistant HIV strains present or suspected. Try to begin regimen within 2 h of exposure (check latest recommendations)
Abnormal bleeding			
Perimenopause/ Menopause	Vaginal dryness	Vaginal moisturisers and lubricants	Oestrogen creams, rings, patches
			0.3 mg conjugated oestrogens, 0.5 mg oestradiol, 0.025 mg transdermal 17β-estradiol
			Premarin 2.5 mg tablets, Premarin 1.25, oestradiol 2 mg
	Menstrual cycle irregularity		
	Stress incontinence	Kegel exercises	
	Hot flushes and night sweats	Layered clothing	Vitamin E; Clonidine patch or pill
		Avoid stimulus (caffeine, other), exercise, eat food with tryptophan	
	Insomnia		
	Irritability/moodiness	Exercise, oestrogen replacement therapy, antidepressants	
	Osteoporosis	Weight-bearing exercise, calcium, vitamin D	
Personal safety	Lessons in self-defence prior to trip	Alarms	
		New hand-held personal alarms	
		Pepper spray	
Breast-feeding		Supplies for lactation	Antibiotics to treat mastitis Ciprofloxacin 250 mg b.i.d. x 14 days
		Breast pump	
		Nipple cream	
Pregnancy		Blood pressure cuff	Antinausea Rx
		Urine protein/glucose strips	Prenatal vitamins

With low-dose formulations a change in schedule could result in ovulation, so pills should be taken according to the home schedule. If a pill is missed, the patient should take it as soon as she remembers and then take the next one at its usual time. Missing two or more pills requires a back-up method for the rest of the month.

Nausea, vomiting or diarrhoea may decrease absorption of the pill. If vomiting occurs within 3 hours of taking a pill, another should be taken. Inability to take a replacement would be equivalent to missing two pills.

No large studies have demonstrated that antibiotics, other than rifampicin, lower steroid blood concentrations [12]. To

Table 25.3 Currently available contraceptive choices for travel

	Mechanism	Advantages/disadvantages	Travel issues
Barrier			
Spermicides: creams, jellies, foams, melting suppositories, sponges, foaming tablets, films	Surface-active agents that damage the cell membranes of sperm, bacteria and viruses	Chronic exposure may cause mucosal injury that increases risk of HIV transmission	Easy to carry Readily available Bring own supplies Female controlled
Cap	Mechanical barrier Requires spermicide	Needs fitting by clinician Can use for up to 48 h Needs practice to use	Easy to carry Rubber may deteriorate in heat and humidity
Sponge	Polyurethane sponge containing nonoxynol-9 Protects for 24 h no matter how many times intercourse occurs Leave in place for 6 h after intercourse	One size Over the counter Moisten with water prior to use and insert Loop for removal Do not wear longer than 24–30 h due to risk of toxic shock syndrome	Easy to carry, use Use bottled water for moistening in countries with questionable water supply
Diaphragm	Domed-shaped rubber cup Must use with spermicide Protection for 6 h	Requires fitting by clinician Insert extra spermicide with repeated intercourse After use leave in for 6 h	Carry in climate-resistant case Spermicide may not be available in developing countries
Condom			
Female (Reality)	Polyurethane pouch Spermicide not required One use only	Can be inserted 8 h before intercourse	Female controlled Bring supply from home Does not deteriorate in heat and humidity
Male	Latex	Possible allergy Do not use oil-based lubricants	Male controlled Quality varies country to country
	Polyurethane	Thinner/stronger, more resistant to deterioration Can use oil-based lubricants	Bring supply from home of latex and polyurethane types
	Lambskin natural	Small pores permit passages of viruses – Hep B, HSV, HIV Use only for contraception Brands and materials differ in quality	May break down in heat and humidity. Carry in special case Use emergency contraception if condom breaks or slips and no back-up method in place (OCP/diaphragm/sponge/etc.) Store in cool, dry place
Hormonal			
Pills			
Progestin only	Inhibition of ovulation (may occasionally ovulate) Thickened and suppressed cervical mucus Suppression of mid-cycle LH and FSH	Use if cannot take oestrogen Take same type of pill every day: no pill-free week Decreased menstrual cramps, less bleeding Can use when breast-feeding, older women, smokers	Need to be prepared for irregular bleeding *Must* take pill at same time every day – set alarm watch to help with time zone changes Must use additional method for protection against STDs (condoms, etc.)

(*Continued*)

Table 25.3 (*Continued*)

	Mechanism	Advantages/disadvantages	Travel issues
Combined pill: oestrogen + progesterone	Inhibition of ovulation Many different types Monophasic (fixed dose of hormones in every pill) Triphasic (dosage of hormones in pills varies week to week)	Increased menstrual cycle regularity Less blood loss Less cramping Fewer ectopic pregnancies Less pelvic inflammatory disease Fewer cysts Fewer fibroids Less endometriosis If nausea and vomiting, need to take back-up method or consider placing pill in vagina for absorption May use as emergency contraception; check instructions Contraindications: blood clots	Convenient, effective, easy to carry Need to take every 24 h Must use additional method to prevent STDs (condoms, etc.) May use to delay menses by starting next packet of active pills following 3 weeks of previous packet Consider drug interactions Bring supply from home Research availability of OCP and/or other method to use if OCP lost or stolen See IPPF guide to hormonal contraception Check Princeton website for availability http://ec.princeton.edu/
Depo-Provera	Intramuscular injection (shot) 150 mg dose administered every 3 months Blocks luteinizing hormone surge and prevents ovulation	Side effects: Weight gain Menstrual irregularities Acne Mood changes Decreased libido Osteoporosis Good for women who cannot take oestrogen	Compliance issues Good if unable to remember OCP Good if travel is for < 3 months Need injection every 3 months – may be difficult to get if travelling Need to be prepared for irregular bleeding
Implanon	Thin, permeable silastic capsules which contain the synthetic progestin levonorgestrel	Menstrual irregularities – varies from unpredictable irregular bleeding to no menstrual period Implants difficult to remove, may be broken No protection against STDs Weight gain, acne, alopecia (hair loss) Contraindications: thrombophlebitis, liver disease, liver tumours, breast cancer, pregnancy	Long-term protection 3–5 years May be difficult to remove when travelling Need to be prepared for irregular bleeding, carry pads/tampons/menstrual cups) Amenorrhoea (lack of menses) may be positive side effect, need fewer menstrual supplies
Intrauterine devices Only two approved for use in US Others worldwide	Inhibition of sperm migration, fertilisation and ovum transport Creates environment that is spermicidal by provoking a sterile inflammatory reaction which is toxic to sperm and implantation	Main risk of IUD-induced infection: at insertion more than one partner increases risk of infection Medical risks: pelvic inflammatory disease STD/HIV risk factors Pregnancy	Good method for women who have already had children, have one sexual partner Good for travel as lasts for 1–10 years depending on type of IUD Need to use additional method to prevent STDs (condoms, etc.) Need to know how to check for string Need to know warning signs and what to do in an emergency

FSH = follicle-stimulating hormone; Hep B = hepatitis B virus: HIV = human immunodeficiency virus; HSV = herpes simplex virus: ITP = idiopathic thrombocytopenic purpura, LH = luteinizing hormone; OCP = oral contraceptive pill; STD = sexually transmitted disease.

Table 25.4 Resources on reproductive options

Resource	Notes
Pregnant Pause [http://www.pregnantpause.org/lex/world02.jsp]	Website provides a list of countries where abortion is legal (and what restrictions are placed on abortion)
Contraceptive Research and Development (CONRAD) Program http://www.conrad.org/general.html	Primary objective is the development of new or improved contraceptives and methods for prevention of the transmission of sexually transmitted infections that are safe, effective, acceptable, and suitable for use in developed and developing countries Links to sites for general contraceptive information
International Planned Parenthood Federation (IPPF) www.ippf.org	Regent's College Inner Circle Regents Park London W1 4NS, UK Tel + 44 (0)207 487 7900 Fax + 44 (0)207 487 7950 Email info@ippf.org
Marie Stopes International http://www.mariestopes.org.uk/Womens_services.aspx	Website provides country information on the availability of emergency contraception, contraceptive methods and abortion, with help line numbers for advice and services related to family planning and sexual health
Office of Population Research Emergency Contraception http://ec.princeton.edu/worldwide/default.asp	Website with information on emergency contraception Click on country of destination to see options that are available in the country Click on 'search EC type' to find out in which countries a particular contraceptive is available
PATH (Program for Appropriate Technology in Health) Consortium for Emergency Contraception http://path.org/	Health information on emergency contraception for providers and patients. Available in many different languages PATH has been designated the WHO collaborating center on research in human reproduction
WHO Gender and Health Technical Paper http://www.who.int/docstore/gender-and-health/pages/WHO%20-%20Gender%20and%20Health%20Technical%20Paper.htm	Excellent paper on the importance of gender with regards to all aspects of health including tropical disease

date there are no known interactions between oral contraceptive pills and malaria chemoprophylaxis. There has in the past been a concern that broad spectrum antibiotics such as doxycycline might reduce the efficacy of oral contraceptives, but the data over the years have not supported this and no back-up method of contraception is now recommended [13, 14].

Emergency contraception

Contraceptive failures are common, thus emergency contraceptive options should be taught. This is defined as a method of contraception that can prevent pregnancy after unprotected intercourse, contraceptive failure or a sexual assault [15].

The emergency contraception options available in most countries include either two doses of oestrogen-progestin combination contraceptive pills or two doses of levonorgestrel pills taken 12 hours apart. Women can obtain information on what options are available in various countries by checking the emergency contraception web site (*see* Table 25.4). Knowing the generic names of the medications will assist in obtaining additional supplies. Doses as low as 10 mg of mifepristone may also be effective and have fewer side effects.

A copper-containing intrauterine device (IUD) is also highly effective. Advantages include its high efficacy, 5-day window for insertion and ongoing contraceptive benefit if it is kept in place.

Unplanned pregnancy

If a traveller becomes pregnant and wishes to terminate the pregnancy it may be best for her to return home. Over half the countries listed by the International Planned Parenthood Federation prohibit abortion except in cases such as rape and life-threatening illness.

The Center for Reproductive Law and Policy web site provides a list of countries where abortion is legal and what restrictions are in place. The Marie Stopes International website gives a list of similar and related services. Another helpful resource is the Emergency Contraception website. www.not-2-late.com.

Risk of venous thrombosis

The risk of venous thromboembolism is small, ranging from 10 to 30 cases per 100,000 per year in women using oral contraceptives, versus 4 per 100,000 in general. Some studies have found no difference in risk with the low-dose second- and third-generation oral contraceptive pill formulations [16]. The risk in pregnancy is much greater, estimated to be 60 per 100,000. Current use of oestrogen replacement therapy has been associated with a two- threefold increase in risk [17, 18].

Women on oral contraceptives should be advised about this risk and taught preventive measures such as exercise and hydration. Aspirin therapy might also help decrease this small risk [19]. A woman with a personal history of a venous thrombosis should not take oral contraceptives. A woman with a strong family history of venous thrombosis might be screened for one of the biochemical or genetic defects associated with an increased risk [20]. Travel to high altitude adds other complicating factors that may need to be considered.

Gender-related issues in tropical disease

During the past few years gender-based research has increasingly emphasised the differences between men and women with regard to disease susceptibility, response to infection, disease manifestations and treatment recommendations. Examples of such in the field of travel medicine include the susceptibility of the pregnant women to malaria and the effects of female genital schistosomiasis.

A recent review from the Geosentinel Network points out that while women are more likely than men to seek pre-travel advice, they are also more apt to suffer from gastrointestinal maladies, respiratory infections, urinary tract infections, psychological stresses, dental problems and adverse reactions to medications. On the other hand, they are less likely to contract vector-borne diseases, leishmaniasis, rickettsioses, viral hepatitis, sexually transmitted diseases and such non-infectious maladies as acute mountain sickness and frostbite [21].

In developing countries, the World Health Organization (WHO) section of the Tropical Disease Research (TDR) programme has formed the Gender and Tropical Disease Task Force to stimulate evaluation of gender determinants in tropical disease. [22]. These include differences in exposure, intensity of infection, morbidity, length of incapacity, care received, access to health services, and impact of illness on productive and reproductive capacity, social activities and personal life. While the focus of the WHO is on women living in endemic countries, we need to consider the possible gender-related effects of these diseases on women travellers.

Parasitic infection

Parasitic worms have been found on Pap smears. Amoebiasis can result in vulvar lesions and unusual vaginal discharge [23]. Breast masses are not always malignant: they can be parasitic in a woman with the appropriate travel history [24, 25]. A case of microfilariae in follicular fluid was recently described in a report of a patient undergoing infertility treatment [26]. Thus, pre-travel advice for a woman should include information about how a particular disease might affect her fertility or pregnancy. After travel, women should be asked about travel history if they have recurrent gynaecological symptoms or are in the process of an infertility work-up or breast-mass evaluation.

Physicians evaluating women immigrants or world travellers for infertility and other gynaecologic problems should consider parasitic infections in the differential diagnosis [27]. In addition, clinicians caring for pregnant women should review the patient's travel history as some tropical diseases will have an accelerated course during pregnancy and some may be congenitally transmitted [28]. Some infections may also cause problems during the perimenopause and menopause.

Therapeutic recommendations for individual conditions

Virtually all the important helminth infections in humans can be treated with one of five anthelmintics currently in use [29]. These drugs are vital not only for the treatment of the individual but are also useful in controlling transmission within a community.

Mebendazole and albendazole are most effective against intestinal nematodes, but the results of animal studies would caution against their use during the first trimester of

pregnancy [30]. Diethylcarbamazine is widely used to treat and control lymphatic filariasis, and there is no evidence of fetal harm in pregnancy, but adverse effects related to death of microfilariae or damage to adult worms may be marked [31, 32]. Ivermectin is used in the treatment of onchocerciasis and is undergoing investigation for use against lymphatic filariae. Pregnancy data regarding this drug are reassuring [33]. Praziquantel, used to treat schistosome infections, is also effective in other trematode infections and adult cestode infections and appears to be safe in pregnancy [34].

Female genital schistosomiasis

An increasing number of women are exposed to schistosomiasis through adventure travel or working in endemic areas [35]. Women, therefore, need to be educated about the risks of such exposure.

Female genital schistosomiasis (FGS) is characterised by the presence of schistosome eggs or worms in the genital tract [36]. Schistosoma ova and adult worms have been detected throughout the female genital tract from the vulva to the ovaries [37]. Estimates from postmortem studies in endemic areas show frequencies of anywhere from 7 to 100% for lesions in the lower reproductive tract, and 2 to 83% for lesions in the upper reproductive tract. FGS may also be an important factor in the spread of sexually transmitted diseases, especially AIDS. Because lesions tend to bleed easily, HIV in semen would have access to the blood circulation via ulcerative lesions [38]. These observations have led the Gender Task Force to include FGS in a list of scientific areas that deserve a high research priority [39].

FGS symptoms and signs are non-specific: irregular menstruation, pelvic pain, vaginal discharge. Lesions may take months or years to develop. In the vagina or vulva they may lead to hypertrophy and obstruction. They may be painful or painless, and may result in fibrosis of the ovaries, tubal occlusion, ectopic pregnancies and infertility. Infection of the placenta may cause stillbirths.

Diagnosis is usually made by visualisation of lesions and biopsy led by a high index of suspicion. Less invasive means of diagnosis are needed.

Amoebiasis

Among parasitic diseases, only malaria and schistosomiasis result in more deaths than amoebiasis. The prevalence of colonic disease is equal in men and women, but extraintestinal disease is 3–10 times more common in men. However, children, especially neonates, pregnant women and women in the postpartum period have an increased risk for severe disease and death [40]. There is no evidence that *Entamoeba histolytica* is associated with an intrauterine infection; however, passage of infection from mother to infant may occur during delivery or the neonatal period.

Trypanosomiasis

Chagas disease is now making its appearance in the US as immigration from Latin America increases. Pregnant women with chronic *Trypanosoma cruzi* infection may present with cardiac or gastrointestinal symptoms and transmit the infection to their fetuses [41].

African trypanosomiasis is an unusual but well-documented cause of fever in returning travellers [42]. A review of cases occurring in the US suggests that disease is nearly always of the East African form, a fulminant illness for which prompt diagnosis is necessary. Travellers visiting areas of endemicity should undertake appropriate measures to prevent tsetse fly bites.

Leishmaniasis

Visceral leishmaniasis is endemic to several tropical and subtropical countries, and also to the Mediterranean region. It is usually transmitted by the bite of a sand fly but occasional non-vector transmissions have also been reported by such means as blood transfusions and sexual intercourse. According to the WHO, the ratio of subclinical to clinical leishmania infections is 5:1.14. Asymptomatic persons may be a reservoir of leishmaniasis for extended periods and patients may develop the disease even decades after travelling to endemic areas.

Pregnancy seems to reactivate even latent disease and worsen its course with worse outcomes for both mother and child, and transplacental infection has been reported even many years after the primary infection [43–45]. Because of this, treatment during pregnancy is advocated despite the toxicity of the medications involved, but some success has been experienced with lower than standard doses [46].

Pregnancy

Pregnancy presents unique risks and potential complications for the travelling woman. Although pregnancy is a normal state of health, it is an altered state of health. With careful preparation, however, most trips can be safely accomplished.

Pre-travel evaluation

(*See* Table 25.5).

Individual recommendations will depend on the details of both the proposed itinerary and the pregnancy itself. An early ultrasound will help to establish the gestational age of the

Table 25.5 Pretravel checklist and risk assessment for pregnant travelers

Stage of gestation
- Establish a reliable due date

Obstetric risk factors
- Ultrasound to rule out abnormalities

Medical risk factors
- Check for immunity to infectious diseases (depending on likely exposure)
  - Syphilis (RPR, VDRL, etc.)
  - HIV
  - Hepatitis A and B
  - Rubella
  - Varicella
  - Measles
  - Pertussis
  - Toxoplasmosis
  - Cytomegalovirus
- Blood count and blood type

Update routine immunisations
- Tetanus/diphtheria
- Influenza
- Polio
- Hepatitis B
- TB skin test

Destination risk considerations
- Due to infectious disease
  - Chloroquine-resistant *Plasmodium falciparium* malaria
  - Outbreak of disease requiring a live virus vaccine
  - Outbreak of a disease for which no vaccine is available but has a high risk of maternal and fetal morbidity and mortality
- Due to food water exposure
- Due to insect exposure
- Due to environment
- Sports or exercise risk
  - Altitude
  - Open water
  - Lack of access to care
  - Travel risk assessment
- Mode of travel
- Medical services available during transit and at destination

Medical insurance and evacuation coverage

Review emergency signs and symptoms for which care should be sought
- Headache, aches and pains
- Pelvic and abdominal pain
- Bleeding
- Rupture of membranes
- Contractions
- Signs and symptoms of toxaemia – proteinuria, severe headache with visual change, severe oedema and/or accelerated weight gain
- Vomiting, diarrhoea, dehydration
- Thromboembolism
- Food and water precautions
- Abdominal pain

Recommendations
- Immunisations to reflect actual risk of disease and probable benefit
- Medications – review safety during pregnancy

Preventative measures to decrease:
- Gestation-related risks
- Typical problems
- Mode of travel risks
- Food-related risk
- Water-related risk
- Insect-related risk
- Environment-related risk
- Sexual-behaviour risk

Medical kit adaptations

Paperwork
- Passport, visa, immunisation record
- Check airline regulations (usual limit <36 weeks)
- Letter confirming due date
- Copy of medical records
- Letter for customs regarding medications
- Exemption letter/waiver for vaccines
- Proof of marriage and spouse's permission to travel (if travelling alone)

Preparing for obstetrical care
- Check coverage by medical insurance
- Arrange travel insurance
- Arrange medical assistance
- Arrange for obstetrical care at destination

Comfort arrangements
- Loose clothing and shoes
- Pillows, support stockings
- Bottled water
- Upgrade flight seating if possible
- Upgrade hotel accommodations
- Lighten itinerary

Postpone travel if risks outweigh benefits

pregnancy and rule out problems such as an ectopic pregnancy or multiple gestation. Laboratory data should include blood type and Rh factor. Checking for immunity to various infectious diseases may obviate the need for some vaccines. Serology for toxoplasmosis, rubella, measles, chickenpox, cytomegalovirus and hepatitis B should be considered.

The medical and obstetric history should be reviewed carefully, with particular attention to gestational age and evaluation for high-risk conditions.

Extra documentation may also be needed. Airlines and cruise companies restrict travel after 36 weeks and sometimes as early as 28 weeks, which is the standard cutoff for

cruise lines [47]. The pregnant traveller should be provided a copy of her prenatal record and her physician's telephone number, fax number and email address.

In consideration of the usual discomforts of pregnancy, the traveller may benefit from an upgrade in airline seating and should seek convenient and practical accommodations (i.e. close proximity to the toilet). A realistic and slower-paced itinerary will lessen fatigue and dependable travel companions can assist in the case of an emergency.

Preparation also includes educating the patient regarding the management of minor pregnancy discomforts such as oedema, abdominal bloating, haemorrhoids, urinary frequency, headache and nausea. In addition, the diagnosis and management of more serious complications should be discussed. A recommended medical kit for the pregnant traveller is outlined in Table 25.12.

Relative contraindications for travel during pregnancy

Although travel is rarely contraindicated during a normal pregnancy, complicated pregnancies require extra consideration (*see* Table 25.6).

Some complications may be managed adequately to allow safe travel during pregnancy, particularly when there is advanced obstetric care available at the destination. Conditions that fall into this category include multiple gestation, malpresentations, fetal growth restriction or hyperemesis gravidarum. Other examples where limited travel may be safely undertaken with proper preparation include medical complications such as diabetes, hypertension and anaemia.

When a small amount of bleeding occurs (less than a normal menstrual period) it may presage a miscarriage, but more often is harmless [48]. In this case the usual advice is 24 hours of bed rest. Bleeding in larger amount, however, demands prompt medical attention. It should also be remembered that if the patient's blood type is Rh negative, she will need Rh immune globulin, and this may not be available in many areas [49]. For this reason, and in case of haemorrhage, the pregnant women should travel with documentation of her blood type.

Premature labour and premature rupture of the fetal membranes are two conditions that also require prompt medical attention [50, 51]. Unfortunately, both conditions can be very difficult to accurately diagnose. A reliable sign of truly ruptured membranes is the constant or repetitive leakage of fluid sufficient to run down the legs. Premature labour is even more difficult to diagnose, as the contractions of false labour may be just as regular and painful. A vaginal examination is often necessary to determine the difference. True contractions, whether false labour or true labour, can usually be felt externally by placing one's hand on the abdomen. If the patient is experiencing six or more painful contractions in one hour she should seek medical attention. Meanwhile, vigorous oral hydration or a warm bath or shower may suffice to slow the contractions.

There are some conditions when any travel would be contraindicated, particularly when events could occur in transit that would threaten the lives of both mother and infant. Second or third trimester bleeding, for instance, whether due to abruption or placenta previa, could progress to unstoppable haemorrhage during transport. In the first trimester, an ectopic pregnancy could pose a similar danger, as could an incomplete abortion. Premature rupture of the membranes or premature labour may lead to delivery in an uncontrolled situation such as in a moving vehicle or during an airline flight. Similarly, severe toxaemia may result in seizures. In such cases it is much more preferable to transport appropriate help to the patient than to transfer the unstable patient herself.

Options for emergency care

Obstetric emergencies, when they occur, are often sudden and life threatening. Prior to travel, arrangements should be made for obstetric care in the destination country should it become necessary. Comprehensive medical and evacuation insurance is highly encouraged, while keeping in mind that many insurers exclude pregnancy-related problems. Insurance policies must be reviewed carefully to make sure that they cover the expenses associated with a normal pregnancy together with the possible complications of pregnancy. The policy should also cover expenses associated with care of the neonate (see Table 25.7).

Medical evacuation arrangements should be made in advance of travel. An agency qualified to handle obstetric emergencies will have a standing arrangement with a perinatal team, including a physician and a nurse trained in high-risk obstetric and neonatal care. In addition, they should have expertise in emergency air transportation of pregnant patients.

As pointed out above, in some situations it is safer to transport appropriate help to the patient than to attempt to transport an unstable patient in an unstable environment. A skilled and experienced perinatal team will know best how to judge the risk of transport versus providing care locally.

Transportation risks and preventive measures

Air travel

For a healthy pregnant women and her fetus, commercial air travel should pose no extra risk. Air cabins of most commercial jetliners are pressurised to 5,000–8,000 feet (1,524–2,438 m), an altitude that should cause no fetal problems in

Table 25.6 Relative contraindications for travel during pregnancy

Obstetrical risk factors	**Management challenges**
Abnormal presentation	Likely need for caesarean section
Abruptio placentae	Risk of haemorrhage and death en route
Active labour	Risk of uncontrolled delivery en route
Fetal growth restriction	Risk of fetal hypoxia at altitude or in flight
Incompetent cervix	Risk of premature delivery
Multiple gestation	Risk of premature delivery
Placenta previa or other placental abnormality	Risk of haemorrhage and death en route
Premature rupture of membranes	Risk of uncontrolled delivery en route, cord prolapse, infection
Suspected ectopic	Risk of rupture and death en route
Threatened abortion, vaginal bleeding	Risk of haemorrhage and death en route
History of miscarriage or ectopic pregnancy	Risk of recurrence should be ruled out prior to travel
Toxaemia, past or present	Risk of seizures, aspiration, abruption, uncontrolled delivery
History of infertility	Increased risk of complications. Psychological challenges in case of pregnancy loss
Premature labor	Risk of premature delivery
Maternal age <15 or >35	Increased risk of complications
Medical risk factors	
Anaemia	Risk of fetal hypoxia at altitude or in flight
Diabetes	Need for constant glucose monitoring, insulin dose adjustment. Likelihood of birth complications
Gastrointestinal disease	Risk of diarrhoea, dehydration, ketosis
Heart disease, especially valvular	Risk of cardiac decompensation pre-partum or intrapartum
Haemoglopinopathy	Risk of fetal hypoxia at altitude or in flight
Hypertension	Need for constant monitoring and medication changes. High risk of growth restriction, prematurity, abruption
Pulmonary disease, asthma	Increased risk of pulmonary infections during travel
Seizure disorder	Increased metabolism of medications requires frequent monitoring of drug levels and dosage changes
History of thromboembolic disease	High risk of recurrent thombosis. Requires sub-Q heparin throughout pregnancy with constant laboratory monitoring
Thyroid disease	Need for frequent drug levels and dosage changes.
Other medical disease requiring ongoing assessment and treatment	Need for specialist care and appropriate medications
Destination risk factors	
High altitude	Remoteness from care. Possible risk from hypoxia
Scuba diving	Risk of decompression illness in fetus
Areas endemic for, or where epidemics are occurring of, life-threatening food- or insect-borne infections	Maternal illness may be worse due to pregnancy physiologic factors, or more difficult to treat
Areas where chloroquine-resistant *Plasmodium falciparum* is endemic	Increased risk of severe maternal illness and potential for fetal death
Areas where live vaccines are required and recommended	

a normal pregnancy but requires extra care in complicated ones (*see* section on Altitude, below.)

Air travel also presents other risks, including exposure to infectious disease, immobility and the common discomforts of flying. Abdominal distension, for instance, becomes a greater problem as air pressure decreases. Pedal oedema frequently occurs on long flights – loose clothing and shoes should be recommended.

Deep vein thrombosis (mentioned above) may be problematic due to alterations in clotting factors and the pressure

Table 25.7 Agencies for medical assistance and pregnancy information

Agency	Address	Comments
SOS/AEA International	4050 Columbia Seafirst 701 5th Ave Seattle, WA 98104–7016, USA; Phone: 800 468 5232 206 340 6000; Fax: 206 340 6006 8 Neshaminy Interplex Suite 207 Trevose, PA 19053 6956, USA; Phone: 800 523 6586 215 245 4707	Medical evacuation, repatriation, medical referral, 24 h medical services Alarm centres located around the world Subscribers have access to services worldwide Global coverage
Credit card and insurance companies, banks		American Express, Bank America
International Association for Medical Assistance to Travelers (IAMAT)	417 Center Street Lewiston, NY 14092, USA; Phone: 716 754 4883 40 Regal Road Guelph, Ontario MGE 1B8, Canada	Directory listing of IAMAT centers throughout the world furnishes the names of physicians
Internet/WWW OBGYN.net	www.obgyn.net Europe, South America, USA	Country-specific information on associations, hospitals, research, medical schools, culture and much more Made possible through the efforts of OBGYN.net international representatives
Local US, Canadian or British embassy or consulate	Respective countries	Provide names of physicians in the area
Local medical school or university		For English-speaking physicians
SAFEtrip	PO Box 5375 Timonium, MD 21093, USA; Phone: 800 537 2029 410 453 6300; Fax: 410 453 6301; Email: medexasstr@aol.com	Offered by MEDEX Assistance Corporation Provides emergency assistance, close monitoring of treatment, evacuation, and others
World Health Organization	http://www.who.int/ith/en/	Developing section focusing on issues pertinent to woman travellers Mobile health offerings, such as the Medicine Translator and regional health news and alerts, provide travellers with access to needed healthcare tools and services
Reprotox	http://reprotox.org/	An exhaustive, constantly updated reference of drugs and chemicals and their effects on fetal development. Membership required.
American College of Obstetricians & Gynecologists	http://www.acog.org	Official statements of opinion on almost any pregnancy-related issue, based on best available evidence. Membership required
US DOT Office of Aviation Medicine	http://www.asma.org/	Information regarding aviation and medicine
The Pregnant Traveler	http://www.pregnanttraveler.com	A privately operated web resource with extensive bibliography related to pregnancy and travel

of the expanding uterus. Preventive measures should include frequent stretching, walking and isometric leg exercises. An aisle seat would facilitate this activity. In addition, the patient may consider using an exercise device such as the Airogym or wearing compression stockings. Pregnant women should also be encouraged to drink non-alcoholic beverages to maintain hydration and placental blood flow [52].

The radiation exposure associated with a long flight has been estimated to be the equivalent of one chest radiograph. Most experts feel that this amount of radiation poses little threat, but for pregnant travellers who are frequent flyers this may be a consideration [53]. Airport security machines of any type are not felt to be harmful to the fetus.

Motor vehicle travel

Motor vehicle accidents are a common cause of maternal and fetal morbidity. Unfortunately, lap belts have been associated

with placental and fetal injury. A diagonal shoulder strap with a lap belt provides the best protection, with the straps carefully placed above and below the 'abdominal bulge'. Pregnant women on an extended automobile or bus ride should take frequent exercise breaks to prevent venous stasis.

Sea voyages

The most apparent health risk associated with sea voyages is the exacerbation of the nausea and vomiting associated with pregnancy. The pregnant patient planning a cruise should also be advised of the risk of falls on a moving vessel. The patient should be reminded of common infections encountered on cruise ships such as influenza and gastroenteritis, and frequent hand washing should be stressed. Lack of access to medical care in case of an emergency is another issue, especially on smaller vessels. Most cruise lines restrict travel beyond the 28th week of pregnancy.

Other modes of transportation

Bicycles and motorcycles present the added risk of direct trauma to abdomen and fetus. These modes of transportation should be eschewed or helmets should be used and high speeds avoided. Similar precautions apply to riding horses or other animals.

As with all close human exposure, using buses or trains may expose the pregnant woman to infectious diseases. When possible, pregnant women should be advised to sit in uncrowded areas and avoid exposure to small children. If culturally appropriate, a mask or a shawl across the face may be used and, again, the need for frequent hand washing cannot be overstressed.

Avoidance of common travel-associated illnesses

Travellers' diarrhoea

Some illnesses are more common and more severe during pregnancy and require strict preventive measures as well as prompt treatment. An enlightening example is travellers' diarrhoea, amounting to an incidence of 50% and higher in travellers to some destinations. Decreased gastric acidity and slowed intestinal transit, both of which would enhance the persistence of the bacteria, not only make diarrhoea more likely but increase the risk of severe disease with complications such as dehydration and ketosis [54]. Biochemical changes also mean that diarrhoea will result more quickly in acidaemia. The combination of this and dehydration may then lead to premature labour, hypovolaemic shock and even fetal death [55–57].

The usual recommendations consist of strict hygiene and food and water precautions, to be supplemented by vigorous oral hydration should the problem occur. Alcohol-based hand-sanitisers are effective and convenient and may increase proper hand hygiene. Boiled or bottled water is preferable to chemically treated or filtered water. One caveat would be that caution needs to be used in the case of iodine-containing compounds or filters for water purification. Although these are generally felt to be safe and minimal iodine is released into the water during their use, some experts have expressed concern regarding the possible suppression of the fetal thyroid [58, 59].

When diarrhoea does occur the treatment of choice is prompt and vigorous oral hydration. The traveller can take pre-mixed oral rehydration powders with her or oral rehydration therapy (ORT) packets may be purchased locally. Although they may become necessary, intravenous fluids should be avoided, particularly in environments where sterile equipment cannot be guaranteed.

Loperamide does not increase the risk of congenital anomalies or adverse pregnancy outcomes, but it slows intestinal motility and is not recommended for prophylactic use. It might be considered for treatment in moderate to severe cases [60]. Bismuth salicylate, however, is felt to be contraindicated in pregnancy as the routine use of salicylates is not advised, and bismuth has been known to cause fetal encephalopathy and fetal hypotonus in pregnancy [61, 62].

Prophylactic antibiotics are not recommended, but treatment doses may be needed in severe cases. The fluoroquinolones for many years have been felt to be contraindicated, but recent studies have demonstrated their safety during pregnancy [63, 64]. Rifaximin has in recent years been increasingly used and animal studies would seem to indicate its safety in pregnancy [65, 66]. As it is not absorbed systemically, it might be considered to be safer than other drugs. Some experts have expressed concern that this medication might alter intestinal flora sufficient to interfere with nutrient absorption, but this too has yet to be shown by any data. Cotrimoxazole is commonly used in pregnancy but its usefulness may be diminished by changing resistance patterns [67].

Erythromycin and azithromycin are safe to take during pregnancy and are especially effective in treating *Campylobacter*-induced travellers' diarrhoea. Second- or third-generation cephalosporins have also been suggested as alternatives. Ampicillin can be used for travellers' diarrhoea, although resistance is becoming widespread.

Probiotics, 'good bacteria', have been shown to be of some benefit in treatment of travellers' diarrhoea but have not been studied for prevention [68].

Respiratory infections

Due to the frequency of respiratory infections occurring during travel, influenza and pneumococcal vaccines might be regarded as 'pre-travel' vaccines. Nasal decongestants should be used sparingly as the uterine arteries are especially sensitive to vasoconstrictors.

Viral hepatitis

Viral hepatitis is of concern during pregnancy [69, 70]. Hepatitis A has been reported to increase the risk of placental abruption and premature delivery. Hepatitis E, also spread by faecal–oral transmission, is a major threat during pregnancy and may result in a case fatality rate of 15–30%. When acquired during the third trimester it is also associated with fetal complications and fetal mortality.

Maternal infection with hepatitis B presents the risk of transmission to the neonate. Vaccination is recommended for all non-immune patients. As hepatitis C and HIV are transmitted through similar means, women should be instructed to avoid high-risk activities that could result in exposure. There is no evidence that pregnancy alters the natural history of hepatitis C or that it interferes with normal pregnancy, and vertical transmission is uncommon [71]. Immune globulin is not thought to be effective post exposure.

Intestinal parasitic diseases

Parasitic diseases are less common but may cause concern, particularly in women who are visiting friends and relatives in developing areas. In general, intestinal helminths rarely cause enough pathology to warrant treatment during pregnancy. Most intestinal helminths, in fact, can safely be addressed simply with symptomatic treatment until the pregnancy is over. Only severe cases, i.e. continued diarrhoea leading to malnutrition, require immediate therapy.

On the other hand, protozoal intestinal infections, such as giardia, amoeba and cryptosporidia, often do require treatment. These parasites may cause acute gastroenteritis, chronic malabsorption resulting in fetal growth restriction, and in the case of amoeba, invasive disease including amoebic liver abscess and colitis. One study reported that two-thirds of the fatal cases of amoebiasis occurred in pregnant women [72, 73]. Vertical transmission of invasive disease may occur independent of maternal symptoms, causing clinical disease in the child either directly after birth or during the first months of life [74].

Although congenital schistosomiasis has been demonstrated in animals, no transplacental transmission has been found in humans. Nonetheless, because this disease may contribute to low birth weight, pregnant women are best advised to avoid swimming or wading in potentially contaminated bodies of fresh water [75].

Listeria and toxoplasmosis

Two other infectious diseases that deserve special attention are listeriosis and toxoplasmosis [76, 77]. Both of these infections are food-borne, most commonly in soft cheeses and raw or undercooked meats. Toxoplasma infection may also occur from handling cat litter or soil in which cats have defaecated.

The risk during pregnancy is that the infection will cross the placenta and cause spontaneous abortion, stillbirth, hydrops fetalis or congenital infection. Risk of fetal infection increases with length of gestation but severity of infection is decreased.

The patient should be warned, therefore, to avoid unpasteurized cheeses and undercooked meat products and instructed to wear gloves if working in the soil or with cat litter.

Environmental considerations

Air pollution

Air pollution, an increasingly common phenomenon worldwide, may cause more health problems during pregnancy as ciliary clearance of the bronchial tree is slowed and the mucus more abundant [78]. Avoiding areas and times of high air pollution is advisable. When unable to avoid polluted areas, wearing a scarf may be of assistance, although fine particles and ozone inhalation will not be prevented.

Heat and humidity

Body temperature regulation is not as efficient during pregnancy and temperature extremes cause greater stress on the gravid woman [79]. In addition, an increase in core temperature such as with heat prostration or heat stroke may be harmful to the fetus [80]. The vasodilating effect of a hot environment might also cause fainting. For these reasons accommodation should be sought in air-conditioned quarters, or at least activities restricted in such environments.

Altitude

The normal physiologic response to increased altitude is hyperventilation. A pregnant woman is already hyperventilating and her cardiovascular system is working harder [81]. Therefore, a pregnant woman who travels to high

altitude may experience exaggerated breathlessness and palpitations. In addition, diuresis may further predispose to thrombosis.

Some studies of populations living at high altitudes have shown a tendency towards small-for-dates infants; however, short exposure to moderate altitudes appears to have no adverse effects on the woman or the fetus [82, 83].

The fetal circulation and fetal haemoglobin protect the fetus against hypoxia as fetal haemoglobin allows a greater extraction of oxygen. These compensatory mechanisms may be inadequate, however, when the pregnancy is already complicated by maternal anaemia or placental insufficiency. Further, the uterine architecture is already complete by mid-pregnancy and the uterus itself has little physiologic capability to adjust to extreme physiologic changes. Also, fetal bradycardia has been seen with exposure to extreme altitudes. Therefore, travel to more than moderate altitude should be avoided.

Even brief excursions to higher altitudes may result in acute mountain sickness (AMS). The common symptoms of AMS (insomnia, headache and nausea) are frequently also associated with pregnancy and it may be difficult to distinguish the aetiology of the symptoms.

The best prevention is a gradual acclimatisation to the altitude. Acetazolamide has long been used in pregnancy for the treatment of pseudotumour cerebri and is felt to be safe, despite some conflicting animal data [84–86]. Also, there is a case report of fetal metabolic acidosis in a mother taking this medication [87]. Although there may be occasions when there is compelling reason to use this medication, most experts recommend simply a slow ascent with adequate time for acclimatisation.

Probably the greatest concern regarding high-altitude travel in pregnancy, however, is that many high altitude destinations are remote from medical care. Altitude travel may not increase the risk of obstetric emergencies, but when they occur, prompt intervention is needed. If a pregnant woman is planning to travel to a high-altitude destination, therefore, it is wise to plan for obstetric emergencies should they occur.

Activities and exercise during pregnancy and travel

The data available indicate that healthy fit women with normal pregnancies can begin or continue a regular programme of aerobic exercise during pregnancy. In fact, improved outcomes for mother and fetus are associated with regular weight-bearing exercise [88].

Nonetheless, the pregnant traveller should be discouraged from undertaking *unaccustomed* vigorous physical activity. Although the American College of Obstetricians and Gynecologists (ACOG) has eased some of its restrictions on exercise during pregnancy, the supporting data were collected under carefully controlled conditions with constant medical supervision [89, 90]. The guidelines may be too restrictive, however, for some women who exercise on a regular basis. Most researchers support a more flexible approach to exercise during a normal pregnancy.

Physiologic changes due to pregnancy should be considered when planning activities. For example, a pregnant traveller who wants to go on a ski vacation should consider the fact that changes in her body's centre of gravity and increased joint laxity may put her at risk of an accident due to a change in balance. Most pregnancy complications would indicate further limitations of activity.

Water sports during pregnancy

Swimming and snorkelling during pregnancy are generally safe, but water-skiing has resulted in falls with injection of water into the birth canal [91].

Most diving organisations such as the Undersea and Hyperbaric Medical Society advise against scuba diving for pregnant women. A review of physiological changes concluded that pregnant women should refrain from diving due to a risk of fetal gas embolism during decompression [92]. The fetal circulation excludes the filtering action of the pulmonary circulation so the fetus may be particularly at risk for gas emboli [93].

A few researchers have suggested that shallow diving, not requiring decompression (less than 10 m), is not associated with abnormal outcome unless frequent and occupationally related. But in women who dive regularly there is evidence of a three- to sixfold increase in incidence of spontaneous abortion and congenital malformation. Until more data are available, scuba diving should not be recommended during pregnancy. Nonetheless, there are case reports of normal pregnancies in spite of continued diving.

Trauma during pregnancy

Trauma assumes greater importance during pregnancy, not only because it is more likely to occur, but also because it is more difficult to triage and treat. Loss of balance and lack of coordination increase the risk of falls. In addition, vascular dilation and ligamentous laxity increase the risk of injury to the woman. At the same time, emergency personnel tend to be very hesitant to undertake even routine investigations and procedures in the pregnant woman. In fact, treatment delay in pregnant women has been shown to increase the risk of fetal and maternal death [94].

Pregnancy-related changes in immune status

Pregnancy results in a number of changes in the maternal immune system. There is a reduction in cell-mediated immunity. Thus pregnancy has been found to result in increased susceptibility to a number of infections in which the cell-mediated immune response is the most important. Examples of this type include malaria, amoebiasis, coccidiomycosis, leishmaniasis, leprosy, listeriosis and tuberculosis [95, 96].

By contrast, infections in which the humoral response is the most important show no increase in susceptibility. B lymphocyte cell numbers and functions do not appear to be reduced during pregnancy.

Vaccines

General considerations

Vaccination in pregnancy often produces anxiety in both the patient and her provider. There is reason for caution, yet it should be remembered that none of the currently available vaccines is known to harm the fetus while many of the diseases they prevent are clearly harmful. Both the ACOG and the CDC emphasise that the benefits of immunisation outweigh the theoretical risks involved [97, 98].

While the primary goal of vaccination during pregnancy is, of course, to protect the mother, the most effective way of protecting the infant against many diseases is to immunise the mother [99–103].

When considering vaccination for the pregnant traveller, both safety and efficacy must be taken into account as well as the risk:benefit ratio. Factors include the incidence of the disease along the itinerary, the risk of acquiring the disease, the risk of treatment of the disease during pregnancy, the known effectiveness of the vaccine both in general and in pregnancy, and the theoretical risk of the vaccine to the mother or the fetus.

Table 25.8 outlines the currently available vaccines and their use in pregnancy. Vaccines using inactive viruses, inactivated bacterial toxins (toxoids), inactivated bacteria or bacterial components are thought to be of low risk for the pregnant woman and her fetus. Live attenuated viral vaccines and live bacterial vaccines are not generally recommended to pregnant women, although limited data suggest that many of these vaccines may be safe. In general, however, live vaccines should be used during pregnancy only if the risk of exposure outweighs a theoretical risk of the vaccine. Agencies where up-to-date information may be found or cases reported are listed in Table 25.9.

As high fever during the first trimester has been associated with neural tube defects and some vaccines may cause a febrile response, precautions may be taken to prevent post-vaccination fever.

Sometimes the need for the vaccine may be obviated simply by a modification of the itinerary, or if the vaccine is recommended simply due to local regulations the patient may be given a waiver letter.

Because of the immune changes that occur with pregnancy there is concern that vaccination may not produce an adequate immune response. There is evidence that this may be the case with yellow fever and perhaps with hepatitis A vaccines [104, 105]. In addition, pregnancy slows intestinal transit and may increase the risk of gastrointestinal adverse events possible with live oral vaccines such as cholera and typhoid.

Specific vaccines

Tetanus, diphtheria and pertussis (Td & Tdap) Tetanus and diphtheria vaccines are recommended for all pregnant women if they are not already immune. There has been some concern that malnutrition, vitamin A deficiency or malaria chemoprophylaxis might interfere with an adequate immune response, therefore whenever possible the vaccine should be given before the initiation of malaria chemoprophylaxis [106–108].

Current recommendations are less wholehearted in the use of the newer formulation containing pertussis vaccine (Tdap), primarily because of the lack of data. Even though pertussis is not reported to have a worsened course in pregnancy, cases of maternal pertussis have been reported, sometimes with serious neonatal results [109, 110]. Some experts, therefore, advocate using Tdap during pregnancy to prevent pertussis in the newborn [111].

PPD/tuberculin skin testing Although one study demonstrated a decrease in lymphocyte reactivity to tuberculin during pregnancy, other studies have shown no change in the anticipated cutaneous reaction to the test. Mantoux testing is interpreted according to the same criteria as in the non-pregnant. There is no evidence that the skin test has any adverse effects on the pregnant mother or fetus [112].

Pneumococcal vaccine Before the advent of antibiotics, maternal mortality from pneumonia approached 30% and more than 70% of pregnant women with pneumonia went into premature labour. Despite advances in treatment, preterm labour and fetal death still may occur [113]. Thus any recommendation for the use of pneumococcal vaccine is not altered by pregnancy. Patients who might be

Table 25.8 Immunisations during pregnancy

Vaccine	Type of vaccine	Maternal risk from disease	Fetal risk from disease	Maternal risk of vaccine	Fetal risk of vaccine	Comment
Tetanus/diphtheria (Td)	Toxoid	Not affected by pregnancy	Neonatal tetanus	None known	None known	ACOG recommends update during pregnancy. Delay administration past first trimester if convenient. Malaria prophylaxis may interfere with immune response
Tetanus, diphtheria, pertussis (Tdap)	Toxoid	Not affected by pregnancy	Neonatal pertussis	None known	None known	Theoretically safe but data lacking
Tuberculin skin test	Toxoid	Course of tuberculosis not affected by pregnancy	Congenital tuberculosis	None known	None known	Reaction to test appears unaltered by pregnancy
Pneumococcal	Polysaccharide	Disease may be more severe in pregnancy	Premature delivery, fetal death	None known	None known	Consider in splenectomised, immunosuppressed or with sickle cell anaemia
Meningitis	Polysaccharide	Not affected by pregnancy	Depending on severity of maternal illness	None known	None known	
Meningitis	Conjugate	Not affected by pregnancy	Depending on severity of maternal illness	None known	None known	Registry exists for reporting use in pregnancy
Haemophilus B conjugate	Polysaccharide					For high-risk persons
Typhoid	Heat/phenol-inactivated, parental					Avoid in pregnancy due to systemic reaction and febrile response
Typhoid Vi	Polysaccharide	Increased risk of diarrhoea, GI bleeding, perforation	Increased risk of abortion, fetal death	None known	None known	
Typhoid oral; Typhoid (Ty21a)	Live bacterial	Increased risk of diarrhoea, GI bleeding, perforation	Increased risk of abortion, fetal death	Nausea, vomiting, diarrhoea	None known	Theoretical risk of mutation into pathogenic form

Hepatitis A	Inactivated virus; formalin-inactivated vaccine	Possibly increased severity in third trimester	Increased risk of miscarriage or preterm birth	None known	None known	Check titer
Hepatitis B	Purified surface antigen; recombinant, purified hepatitis B surface antigen	Possibly increased severity in third trimester	Miscarriage or preterm birth. Transmission to newborn	None known	None known	Use in pregnancy recommended in non-immune women Pre-exposure and post-exposure prophylaxis indicated in pregnant women at risk for infection; check titre
Influenza	Inactivated virus	Increased morbidity and mortality	Increased risk of miscarriage	None known	None known	ACOG encourages use in all trimesters
Influenza	Live virus	Increased morbidity and mortality	Increased risk of miscarriage	Unknown	Unknown	Use of inactivated vaccine is preferred
Polio (eIPV)	Inactivated virus	Possibly increased disease severity in pregnancy	High mortality rate in neonatal disease	None known	None known	Preferred over OPV in pregnancy
Polio (oral)	Live attenuated virus	Possibly increased disease severity in pregnancy	High mortality rate in neonatal disease	None known	None known	Not recommended for public health reasons Avoid in previously non-immune individuals due to risk of vaccine-associated paralysis ACIP recommends use in outbreak situation
Japanese encephalitis	Inactivated virus	Animal data suggest adverse pregnancy outcome	Embryofetal death common in animals. No human data	Some reports of serious adverse reactions unrelated to pregnancy	None known	Vaccine being withdrawn from market
Japanese encephalitis	Live attenuated virus	Animal data suggests adverse pregnancy outcome	Embryofetal death common in animals. No human data	Unknown	Unknown	No data available on use in pregnancy
Rabies	Killed virus	100% fatality	Fatal to fetus if mother dies	None known	None known	Pre- and post-exposure schedule same as in non-pregnant
Rabies immune globulin	Immune globulin	100% fatality	Potentially fatal to fetus	None known	None known	Dosage schedule same as in non-pregnant

(*Continued*)

Table 25.8 (*Continued*)

Vaccine	Type of vaccine	Maternal risk from disease	Fetal risk from disease	Maternal risk of vaccine	Fetal risk of vaccine	Comment
Human papilloma virus (HPV)	Inactivated virus	Rapid growth of condylomata in pregnancy	Viral transmission to fetus	None known	None known	Use of other methods of STD prevention is preferred
Mumps	Live attenuated virus	Not affected by pregnancy	Possible increased rate of miscarriage	None known	None confirmed	Use only if exposure is likely and unavoidable
Measles	Live attenuated virus	Not affected by pregnancy	Increased miscarriage. Possible congenital anomalies	None known	None confirmed	Use only if exposure is likely and unavoidable
Rubella	Live attenuated virus	Not affected by pregnancy	High rate of miscarriage and multiple congenital anomalies	None known	None confirmed	Use only if exposure is likely and unavoidable Registry exists for reporting use in pregnancy Check titer if immunity unknown May give immune globulin if exposure
Varicella	Live attenuated virus	Increase in severe pneumonia	Congenital varicella in second and third trimesters	None known	None confirmed	Use only if exposure is likely and unavoidable Registry exists for reporting use in pregnancy Check titre if exposed during pregnancy Give varicella zoster immune globulin if nonimmune If symptoms treat with aciclovir IV or orally
Herpes zoster	Live attenuated virus	Not affected by pregnancy	Possible congenital varicella syndrome	No data available	No data available	Dose of live virus is greater than in varicella vaccine
Yellow fever	Live attenuated virus	Not affected by pregnancy	Depending on severity of maternal illness	Possibly diminished immune response in pregnancy	Vaccine virus may be transmitted to newborn	Use only if exposure is likely and unavoidable. Immune response may be diminished. Post-vaccination titres encouraged

BCG	Live bacterial	Course of disease not affected by pregnancy	Congenital tuberculosis occurs	None known	Possible disseminated infection (theoretical)	Not effective enough to be felt useful
Cholera/diarrhoea	Live bacterial	Diarrhoea more severe, dehydration, acidosis	Increased risk of abortion or premature birth	No data available	No data available	Oral antibiotic prophylaxis for cholera felt to be preferred due to poor efficacy of vaccine
Cholera	Oral killed					Practise strict food and water precautions Avoid areas with cholera epidemics
Cholera	Inactivated injectable					Not recommended in pregnancy
Oral colostrum extract (diarrhoea preventive)	Oral immunobiologic	Diarrhoea more severe, dehydration, acidosis	Increased risk of abortion or premature birth	No data available	No data available	No theoretical reasons to expect adverse effects
Anthrax	Bacterial particles	May be more severe in pregnancy	Increased risk of miscarriage or preterm birth	None known	None known	Prophylactic antibiotics are preferred to vaccination
Brucellosis	Live bacterial	Not affected by pregnancy	Miscarriage and preterm birth	No data	No data	Prophylactic antibiotics are preferred to vaccination
Smallpox	Live virus	Not affected by pregnancy	Not affected by pregnancy	None known	Vaccinia virus may be transmitted to fetus	Use limited to instances of high risk of exposure
Tick-borne encephalitis	Inactivated virus	Not affected by pregnancy	Viral transmission to fetus	None known	None known	Not recommended during pregnancy Practise strict tick-bite precautions
Immune globulins (IG) pooled or hyperimmune	Immune globulins or specific antitoxic serum including antivenin for snake bite, spider bite, diphtheria antitoxin, HB1g, rabies Ig, tetanus Ig, Rh(D) Ig, varicella zoster Ig			None known	Single report of congenital anomaly	Use usually limited to post-exposure prophylaxis

Adapted from Carroll and Williams [220].

Table 25.9 Reporting and referral agencies for the use of certain vaccines during pregnancy

Tdap	Providers who choose to administer Tdap to pregnant women should discuss the lack of data with the pregnant women and are encouraged to report Tdap administrations regardless of the trimester, to the appropriate manufacturer's pregnancy registry: for Boostrix to GlaxoSmithKline Biologicals at 1-888-825-5249, or for Adacel®, to sanofi pasteur at 800-822-2463
Meningitis (MCV4)	Women with exposure to this vaccination during pregnancy can call toll-free 877-311-8972 for information
Hepatitis B	A registry has been organised to monitor the outcomes of pregnancies that have included a hepatitis B vaccination. Women can call, 1-800-670-6126, and learn more online at http://www.motherisk.org.
HPV vaccine	A vaccine in pregnancy registry has been established; patients and health-care providers should report any exposure to HPV vaccine during pregnancy (Tel: 800-986-8999)
Varicella vaccine	NOTE: The manufacturer and CDC have established a Varivax Pregnancy Registry to monitor outcomes of women who received the vaccine 3 months before or any time during pregnancy. Call 800-986-8999
Yellow fever vaccine	To discuss the need for serologic testing, the appropriate state health department or the Division of Vector-Borne Infectious Diseases (telephone: 970-221-6400) or the Division of Global Migration and Quarantine (telephone: 404-498-1600) at CDC should be contacted
Smallpox vaccine	Contact information for the National Smallpox Vaccine in Pregnancy Registry can be found on the internet at http://www.cdc.gov or by calling 404-639-8253

considered for this vaccine would include those who are immunosuppressed, have had a splenectomy or have sickle cell disease.

Meningitis vaccine The incidence of meningococcal meningitis and the course of the disease are not reported to be different during pregnancy than they are at other times. Studies of polysaccharide vaccine (MPSV4) have not demonstrated adverse effects among either pregnant women or newborns. Thus, pregnancy should not preclude the use of this vaccine. There is so far very little data on the use of the conjugate (MCV4) vaccine during pregnancy. Although no adverse events have been reported and there is no theoretical reason to expect any, the data are too limited to make any recommendations.

Haemophilus influenzae type b Haemophilus influenzae type b is an important cause of meningitis and pneumonia in infants. This vaccine has been a model for the protection of infants from bacterial disease through maternal immunization [114]. For women travelling to endemic areas to live, maternal immunisation with Hib conjugate vaccines could be considered.

Typhoid vaccine There is some evidence that typhoid may be a more serious disease in pregnancy, with a noticeably higher incidence of diarrhoea and other complications, as well as maternal death. There is also an increased risk of abortion and fetal death and transplacental infection of the fetus may occur. It is vital, therefore, that the risk of typhoid be minimised in every way possible. Although there are no published data regarding the use of the Vi capsular vaccine in pregnancy, its use is recommended when there is risk of exposure [115]. Because it is a polysaccharide vaccine it is unlikely to cause a febrile reaction.

A report by Mazzone *et al.* showed no harm from use of the oral vaccine during pregnancy [116]. There is at least a theoretical risk, however, that the vaccine strains might replicate and cross the placental barrier, causing fetal harm similar to that seen with *Salmonella typhi.* In addition, decreased gastrointestinal motility along with increased exposure to gastric acid might either decrease the vaccine's effectiveness or enhance the risk of gastroenteritis. And finally, one of the more common side effects of this vaccine is nausea and vomiting, a problem already frequent in pregnancy. For these reasons, these authors prefer the use of the Vi vaccine during pregnancy.

Hepatitis A While it would appear that pregnancy does not worsen the course of hepatitis A, hepatitis A infection during pregnancy may result in serious maternal consequences and fetal loss, and vertical transmission to the fetus has been described [117, 118]. Thus this vaccine is recommended during pregnancy whenever it would be otherwise indicated. Immune globulin is a safe and effective means of preventing hepatitis A but immunisation with one of the new hepatitis vaccines gives a more complete and prolonged protection and would be preferred, even with short duration before travel.

Hepatitis B All pregnant women should be screened for hepatitis B carriage. The course of acute hepatitis B infection

appears to be unaltered by pregnancy [119]. The danger lies in the risk of transmission to the infant. Because of this risk, the ACOG recommends routine administration of this vaccine to non-immune women during pregnancy [120]. Immunisation for hepatitis B will also prevent hepatitis D infection.

Influenza Influenza results in increased morbidity and mortality during pregnancy. The risk increases in the third trimester of pregnancy or in the presence of other underlying conditions. For that reason, vaccination with the inactivated influenza vaccine is now recommended for all pregnant women at all stages of pregnancy [121–123]. As an effective inactivated vaccine is available and there are no data regarding its effectiveness in pregnancy, the live attenuated influenza vaccine (LAIV) is not recommended.

Polio It is important for all pregnant women to be protected against polio. Paralytic disease may occur with greater frequency when infection develops during pregnancy. Anoxic fetal damage has been reported, with up to 50% mortality in neonatal infection. Extensive study of both the live oral and the injectable inactivated vaccine given during pregnancy showed no increase in the incidence of birth defects or other adverse pregnancy outcomes [124, 125]. The enhanced inactivated polio vaccine (eIPV) is preferred for its safety in both the pregnant patient and the community, but the oral polio vaccine is recommended by some experts when immediate protection is needed [126, 127].

Japanese encephalitis vaccine The Japanese encephalitis virus causes embryofetal death in experimental animals and has been known to be passed transplacentally to the human fetus [128]. For that reason, it would seem prudent to vaccinate pregnant women in whom exposure is likely. A new, inactivated vaccine has become available but, due to lack of data, its use in pregnancy is advised only when there is definite risk of exposure. [129].

Rabies Because rabies is almost universally fatal, the consensus has long been that post-exposure rabies vaccination should be used during pregnancy when indicated. Maternal antibody in the circulation of infants born to vaccinated women is presumptive evidence of transplacental passage [130–132]. These facts support the use of pre-exposure vaccination as well when there is a substantial risk of maternal exposure to the disease.

Human papilloma virus vaccine Although not primarily considered a travel vaccine, the risk of exposure to sexually transmitted diseases makes this vaccine worth considering [133]. The vaccine contains inactivated virus and should theoretically be safe in pregnancy. In addition, no adverse events have yet been reported with the inadvertent use of this vaccine during pregnancy [134]. Another consideration recommending the use of this vaccine during pregnancy is vertical transmission of the virus to the fetus at the time of birth. Nonetheless, when other preventive measures against sexually transmitted diseases will suffice, use of this vaccine during pregnancy should probably be delayed until further evidence becomes available.

Tick-borne encephalitis This disease occurs primarily in the summer months in Europe and western Asia and is transmitted both by the bites of ticks and by consuming unpasteurised dairy products. It can result in death or long-term neurological sequelae in as many as 58% of patients [135]. The virus may be transmitted transplacentally but there is little data on the consequences of this or if pregnancy in any way alters the course of the disease. There have been reports of high fever after the administration of the vaccine to young children but this does not appear as common in adults. Still, the manufacturers recommend its use only after careful, individual consideration of the relative risks and benefits.

It is primarily the viral illnesses such as rubella and varicella that have shown the propensity to cause fetal damage during pregnancy. The associated vaccines are live viruses, altered from their original teratogenic form but with the theoretical potential of causing the very pattern of birth defects that they are designed to prevent.

Mumps Mumps, at least, is not associated with any particular pattern of fetal harm [136, 137], but some spontaneous abortions and other fetal anomalies have been reported when it occurs in the first trimester [138, 139]. Nonetheless, administration of the vaccine would be considered preferable to contracting the disease.

Measles Measles also does not produce any established pattern of birth defects, but data from outbreaks would seem to indicate an increased rate of abortion of up to 50% in the first two months of pregnancy and 20% thereafter, as well as a perinatal mortality rate of 10% and possibly fetal anomalies if the disease is contracted during pregnancy [140]. Other studies confirm the risk of serious maternal complications, particularly pneumonia [141]. As with mumps, no adverse maternal or fetal events have been reported following the administration of this vaccine during pregnancy. Due to the increased incidence of measles in children in developing countries, its communicability and its potential for causing serious consequences in pregnancy, some health providers would advise delaying travel of a non-immune woman until after delivery. If a documented exposure to measles occurs, immune globulin may be given to prevent

disease, but this may not be available in many high-risk countries.

Rubella Probably the most feared viral infection during pregnancy is rubella. Pre-vaccine statistics showed an almost 100% incidence of congenital rubella syndrome (CRS) if the disease is contracted in the first trimester and up to 60% in the second trimester [142]. The syndrome consists of ocular and cardiovascular defects, deafness, microcephaly and mental retardation.

As the rubella vaccine is a live virus similar to the rubella virus, there has been fear that the vaccine itself might result in such a syndrome. Despite careful observation, however, no such syndrome has been seen to occur, even though there is evidence of passage of the vaccinated virus to the fetus [143]. Routine vaccination of pregnant women with this vaccine is still not advised, but if there is risk of rubella infection in a non-immune pregnant woman, use of the vaccine is felt to be preferable to contracting rubella during the pregnancy [144, 145]. Routine prenatal screening for rubella immunity should be emphasised.

Varicella Although less widely recognised than rubella, there is a syndrome of congenital defects associated with maternal varicella infection. In addition, this disease can have serious maternal and fetal consequences if contracted late in pregnancy. Congenital varicella syndrome (CVS) is usually characterised by cicatricial scars that follow a dermatome pattern, neurological defects and abnormalities of the limbs. It may also include ocular, muscular and gastrointestinal defects [146]. It is encouraging that there have been no anomalies to suggest CVS in the offspring of mothers receiving this vaccine [147], and the fetal risk of the vaccine should be theoretically lower than that of the wild-type virus. However, only a small number of such pregnancies have been followed to date, and seroconversion in pregnant patients has not been studied. As with rubella, with unavoidable exposure to this virus the vaccine would be considered preferable to the disease. Varicella zoster immune globulin should also be given to a non-immune woman with exposure to varicella.

Herpes zoster Herpes zoster (shingles) is not known to be more common or more severe during pregnancy but as with primary infection with the herpes zoster virus, it may have serious fetal effects. Because the zoster vaccine contains a significantly larger dose of virus than the routine varicella vaccine, however, its use in pregnancy is not advised.

Yellow fever Yellow fever itself does not appear to be more serious during pregnancy or to result in significant adverse pregnancy outcomes. Nonetheless, it is a very serious disease with up to a 50% mortality rate in native populations and thus needs to be avoided during pregnancy.

There are reassuring data from several sources regarding the safety of this vaccine during pregnancy [148], except for one study from a developing country where there appeared to be an increased abortion rate with the vaccine [149]. There is a single report of transmission to the unborn infant of the vaccine-derived virus but such antibodies were not found in 40 other similarly exposed infants [150].

Meanwhile, the efficacy data are conflicting, with some data showing a lower antibody titre when this vaccine is given during pregnancy [151], while a larger study did not show this [152]. It is possible that this difference may be explained by the difference in timing of the vaccination as those in the first study were mostly vaccinated in the first trimester while the other group obtained their vaccination mostly in the later trimesters. Perhaps the relative immune suppression that occurs with pregnancy is more defined later in pregnancy. A difference in nutritional status (and thus immunocompetent status) might also explain this difference. Even the lower titres, however, were not correlated with any diminished protectiveness of the vaccine in terms of increased incidence of disease.

Given this evidence, the consensus remains that if yellow fever exposure is likely and unavoidable during the travel, the vaccine should be given. Under these circumstances, however, it might be wise to obtain a titre to test for immunity. If travel requirements and no disease exposure are the only reason to vaccinate, then it would be preferable to provide the pregnant traveller with an appropriate waiver.

A nursing mother travelling to a yellow fever endemic area should also delay travel as a neonate cannot be immunised because of the risk of vaccine-associated encephalitis. Breastfeeding is not a contraindication to the vaccine for the mother.

BCG Pregnancy does not seem to alter the course of tuberculosis nor the disease to affect the pregnancy other than to perhaps increase the incidence of anaemia [153]. Some investigators have felt that they identified an increased incidence of congenital anomalies [154], but this remains unconfirmed [155]. Nonetheless, tuberculosis is a serious disease even in pregnancy. The BCG vaccine, however, is of limited value in adulthood. Although no harmful effects to the fetus have been associated with BCG vaccine, disseminated infections with other mycobacteria have been reported in the infants of infected mothers and so its use, being a live bacterium, is not recommended during pregnancy.

Cholera and travellers' diarrhoea Diop and colleagues have pointed out the severe risk that cholera presents during pregnancy [156]. There are several oral vaccines either still in

clinical trials or recently on the market for prevention of cholera and, to a lesser extent, travellers' diarrhoea. To date, the benefit from these has been found to be short-lived and incomplete. Although beneficial to the local population in areas where cholera is endemic, their benefit to the casual traveller has been felt to be limited except when the traveller will be working in high-risk areas such as refugee camps [157]. These vaccines have not been tested in pregnancy.

A different type of 'vaccine', marketed so far only in the US, Australia and South Africa, is Travelan. It contains bovine antibodies obtained from the colostrum of dairy cattle specifically vaccinated against the major strains of *Escherichia coli* (ETEC). It is designed to be taken before each meal and clinical trials (as yet unpublished) show it to be up to 90% efficient in preventing diarrhoea in subjects given an oral challenge with ETEC. According to the manufacturer, its use in pregnancy has not been evaluated.

The immune globulins The immune globulins are being decreasingly used as newer, more effective vaccines become available. Generally, these are felt to be safe in pregnancy, but there was one report of a congenital anomaly possibly associated with immune globulin [158]. In addition, because the immune globulins are a human blood product, the possibility of inadvertent disease transmission remains [159]. There remain conditions, however, such as varicella [160] and rabies where post-exposure use of these products is highly recommended, even in pregnancy.

There are some vaccines that are not in common use but the need for which might arise under special circumstances.

Anthrax There is little data regarding the interplay of anthrax and pregnancy, but at least one review estimates that the disease predisposes to miscarriage and preterm delivery [161]. Anthrax vaccine contains a mix of cellular products of *Bacillus anthracis*. In a study of women in the US army who became pregnant shortly after receiving the vaccine there was no increased incidence of adverse pregnancy outcomes [162]. The ACOG primarily recommends various medications for post-exposure prophylaxis [163].

Smallpox Most data regarding smallpox vaccination in pregnancy dates from prior to the eradication of the disease in the 1970s. Infection with the vaccinia virus has been reported in the fetus after maternal immunisation [164]. Because of this concern, the administration of smallpox vaccine is not recommended during pregnancy. However, the smallpox vaccine has not been associated with an increased risk of congenital defects or pregnancy loss.

Brucellosis Brucellosis is known to cause abortion and preterm delivery in domestic animals and to a lesser degree in humans [165]. Vaccination against this disease is commonly given to livestock but its use in humans is usually limited to persons in high-risk occupations. There are no data on its use in pregnant women. Instead, prophylactic or treatment doses of cotrimoxazole or rifampin are recommended.

It is hoped that in years to come there will be vaccines available against other infectious diseases such as malaria and dengue fever. Some such vaccines are in various stages of the research process. In fact, a dengue candidate tetravalent dengue vaccine is in phase II clinical trial [166]. As yet, however, these vaccines are not in general use and there are no data available on their use in pregnancy.

As malaria is a greater concern in pregnancy than at other times it is felt that women who may become pregnant are a prime target for malaria vaccine. One way to accomplish this would be to prioritise such a vaccine, when available, for use in pre-adolescent girls [167]. A similar approach might be appropriate for dengue vaccination.

A hepatitis E virus (HEV) vaccine is in clinical trials (see section on Viral hepatitis) [168].

Medications

(*See* Table 25.10).

General principles

All physicians advising pregnant women should have ready access to relevant print or web-based references that include reviews of the reproductive literature relevant to drugs and immunisations [169]. Several countries have drug classification systems that are based on a hierarchy of estimated fetal risk, which may be helpful, but the best information for actual patient management will usually be obtained by reviewing a more complete source of data.

As with vaccination, use of medications in pregnancy requires consideration of both safety and efficacy. Many of the physiological changes that accompany pregnancy have an influence on drug metabolism as summarised in Table 25.11. As a result, many medications are absorbed, distributed and metabolised differently during pregnancy. The most common outcome is a lowering of the effective serum concentration so that doses may need to be increased in order to be effective. The degree to which this occurs is neither reliable nor constant, however, so that establishing an effective drug level may require actual serum measurements or, more commonly, an empiric adjustment of dosage based on required action and side effects.

Travel-related drugs may also interact with other commonly used medicines, and common mild side effects may become more pronounced. In addition, most drugs transfer across the placenta by simple diffusion and drug transfer

Table 25.10 Medications in pregnancy

Disease to be prevented	Medication	Formulations available	Dosage	Maternal risk from disease	Fetal risk from disease	Maternal risk from medication	Fetal risk from medication	Comments
Malaria	Chloroquine	Tablet	300 mg base (equal to 500 mg of phosphate salt per week)	Increased disease severity	Premature birth, fetal death	Same as non-pregnant	None known	Altered maternal metabolism may require increased dose
Malaria	Mefloquine	Tablet	250 mg weekly; start 1 week before travel and continue for 4 weeks after travel to malarious zone	Increased disease severity	Premature birth, fetal death	Same as non-pregnant; neuropsychiatric reactions 1:15,000–200,000	None proven; safety in first trimester not fully established although CDC approved	Altered maternal metabolism may require increased dose
Malaria	Atovaquone/ proguanil	Tablet	Atovaquone 500 mg + proguanil 200 mg, or atovaquone 250 mg + proguanil 100 mg; 1 tablet daily for 1–2 days before travel and for 1 week after leaving malarious area	Increased disease severity	Premature birth, fetal death	Same as non-pregnant	None found in limited use; safety of atovaquone in pregnancy not established. It is not known whether atovaquone is excreted into human milk. Proguanil is excreted into human milk in small quantities. Based on experience with other antimalarial drugs, the quantity of drug transferred in breast milk is insufficient to provide adequate protection against malaria for the infant	Altered maternal metabolism may require increased dose

Malaria	Doxycycline	Tablet	100 mg daily and for 30 days after exposure	Increased disease severity	Premature birth, fetal death	Same as non-pregnant	Theoretical risk of damage to fetal teeth and bones beyond first trimester	Some guidelines accept use in first trimester
Malaria	Primaquine	Tablet	30 mg daily during exposure and 7 days after	Increased disease severity	Premature birth, fetal death	Same as non-pregnant	Potential for haemolytic anaemia	Cannot test fetus for G6PD deficiency
Malaria	Proguanil and chloroquine	Tablet	Proguanil 200 mg per day, chloroquine 300 mg base per week	Increased disease severity	Premature birth, fetal death	Same as non-pregnant	Potential for haemolytic anaemia	Folate supplements recommended
Malaria	Pyrimethamine-dapsone (Maloprim)	Tablet	Pyrimethamine 12.5 mg and dapsone 100 mg, 1 tablet once a week	Increased disease severity	Premature birth, fetal death	Same as non-pregnant	Potential for haemolytic anaemia	Folate supplements recommended; pyrimethamine should be avoided in the first trimester. Side effects of dapsone include dose-related haemolytic anaemia, more severe in G6PD-deficient individuals, methaemoglobinaemia, agranulocytosis 1:20,000
Malaria	Pyrimethamine-sulfadoxine (Fansidar)	Tablet	Pyrimethamine 25 mg + sulfadoxine 500 mg, 1 tablet once a week					Severe cutaneous reactions 1:5,000 to 1:10,000. Generally not recommended
Insect-borne diseases	DEET	Spray, lotion		Increased attraction for *Anopheles spp.* (and perhaps other species?)	Depends on maternal illness	None known	Rare case reports of toxicity an high maternal doses	High concentrations not recommended

(*Continued*)

Table 25.10 (*Continued*)

Disease to be prevented	Medication	Formulations available	Dosage	Maternal risk from disease	Fetal risk from disease	Maternal risk from medication	Fetal risk from medication	Comments
Insect-borne diseases	Picardin	Spray, lotion		Increased attraction for *Anopheles spp.* (and perhaps other species?)	Depends on maternal illness	None known	Little human data. None reported in animal studies	
Insect-borne diseases	Permethrin	Spray, solution		Increased attraction for *Anopheles spp.* (and perhaps other species?)	Depends on maternal illness	None known	None reported	
Diarrhoea	Rifaximin	Tablet	200 mg three times daily x 3 days	Increased disease severity, acidosis	Potential for preterm birth	Theoretical risk of altering nutrient absorption	Little human data. None reported in animal studies	
Diarrhoea	Probiotics	Liquid, drinking straw		Increased disease severity, acidosis	Potential for preterm birth	None known	None known	Probably safe but of unproven benefit
Diarrhoea	Loperamide	Tablet	4 mg initially then 2 mg after each loose stool up to 16 mg per day	Increased disease severity, acidosis	Potential for preterm birth	None known, but could potentially prolong the illness	None known	Recommended only for serious illness with non-bloody diarrhoea
Diarrhoea	Bismuth subsalicylate	Liquid, tablet		Increased disease severity, acidosis	Potential for preterm birth	Same as non-pregnant	Fetal encephalopathy and hypertonus reported	Not recommended

Diarrhoea	Cotrimoxazole	Tablet	Trimethoprim 160 mg/ sulfamethoxazole 800 mg	Increased disease severity, acidosis	Potential for preterm birth	Same as non-pregnant	Single case of fetal neutropenia reported	Probably safe but of decreasing benefit
Acute mountain sickness	Acetazolamide	Tablet	125 mg daily x 3 days prior to exposure	Symptoms of AMS may be confused with normal pregnancy symptoms	Risk of hypoxaemia if fetus is already compromised	Single case report of metabolic acidosis in pregnancy	None reported	Acclimatisation preferred to medication
Motion sickness	Meclizine	Tablet	25–50 mg before travel	Symptoms may be confounded by nausea of pregnancy	Same as for diarrhoea if maternal vomiting is severe	Drowsiness, dry mouth, constipation, blurred vision	None reported	
Motion sickness	Dimenhydrinate	Tablet	50–100 mg q 6 hours	Symptoms may be confounded by nausea of pregnancy	Same as for diarrhoea if maternal vomiting is severe	Drowsiness, excitation, restlessness, tachycardia	None reported	
Motion sickness	Scopolamine	Tablet, patch	0.4 mg tablet q.i.d or 1.5 mg patch q 3 days	Symptoms may be confounded by nausea of pregnancy	Same as for diarrhoea if maternal vomiting is severe	Blurred vision, dry mouth, confusion. Much patient-to-patient variation in dose response	Fetal heart rate abnormalities at term	A long historical record of safety in pregnancy but should probably be reserved for severe cases
Motion sickness	Pyridoxine and flavouring	Tablet, lollipop, lozenge		Symptoms may be confounded by nausea of pregnancy	Same as for diarrhoea if maternal vomiting is severe	None	None	Commonly used for nausea of pregnancy
Motion sickness	Ginger and flavouring	Powder, drops, lollipop		Symptoms may be confounded by nausea of pregnancy	Same as for diarrhoea if maternal vomiting is severe	None	None	Reports of efficacy are anecdotal. No clinical trials

Adapted from Carroll and Williams [220].

Table 25.11 Pregnancy pharmacokinetics

System	Physiological change	Effect on pharmacokinetics
Cardiovascular	Increased cardiac output by 50% (by increased stroke volume and increased heart rate)	Drugs are distributed at a different rate and in different proportions to different organs
	Plasma volume increased by 45%	
	Extracellular fluid volume increased by 6–8 litres	
	Increased blood flow to skin	Plasma drug concentration decreased
	Increased coagulability	Decreased drug concentration in interstitial fluid
Respiratory	Increased tidal volume by 40% (respiratory rate unchanged. Blood flow unchanged but proportionately less of cardiac output)	Effect on inhaled medication. Some medicines excreted in exhaled air. Increased absorption of topical preparations
Hepatic	Decreased serum albumin (25%)	Alters bound:unbound ratio of different drugs depending on their composition – has an effect on metabolism, excretion and distribution.
	Increased binding proteins	
	Increased hepatic enzyme activity	
Renal	55% increase in glomerular filtration (80% increase in renal blood flow)	More rapid metabolism of many drugs
Gastric	Gastric emptying time increased. Decreased gastric acidity	Increased excretion of some medications. Medication takes longer to get to the small bowel and be absorbed
Intestinal	Small bowel transit decreased	Some medicines are deactivated by gastric acid so less is available for absorption
		Altered absorption of various drugs
		Longer time in the bowel can mean increased absorption
Other	Increased body fat	Fat-soluble medicines affected

Adapted from Carroll and Williams [220].

increases with gestation due to reduced thickness of the placenta.

Treatment of common symptoms that occur during pregnancy

Analgesics that may be considered safe during pregnancy include acetaminophen and, if necessary, narcotics. In one study, aspirin was found to increase the incidence of abruption, and in higher doses may cause gastric bleeding [170, 171]. Non-steroidal anti-inflammatory agents and the Cox-II inhibitors could theoretically cause premature closure of the ductus arteriosus, thus are best avoided during pregnancy [172].

Jet lag can often be minimised by adequate rest prior to departure and immediately on arrival, along with good hydration and eating lightly in transit. Melatonin or sedatives should be reserved for situations where insomnia is truly pathological.

Other common discomforts during pregnancy include headache, pedal oedema, heartburn, abdominal bloating, constipation, haemorrhoids and urinary frequency. Symptomatic treatment may be needed. Loose-fitting shoes and clothing, easy access to the toilet and eating frequent snacks rather than full meals may decrease discomfort. Constipation may require a mild bulk laxative.

It is common for the modern pregnant woman, cautious about the medical establishment, to seek herbal remedies and alternative forms of healthcare. In fact, some women may specifically be travelling to acquire non-traditional care. Use of materials or methods that are of unproven safety during pregnancy should be strongly discouraged.

Motion sickness

Pregnancy itself is often accompanied by nausea and vomiting. To have added to this the symptoms of motion sickness can be quite distressing. Fortunately, there are several simple remedies that often are effective in relieving the symptoms of morning sickness and these same remedies may help to prevent motion sickness. Non-prescription remedies include ginger, which as a powder can be mixed with food or drinks such as tea. It is also available in candy-like lollipops. Similarly, pyridoxine (vitamin B6) has for many years been found to be effective for morning sickness and is available in tablet form as well as lozenges and lollipops. Antihistamines such

as meclizine and dimenhydrinate are often used in pregnancy and appear to have a good safety record [173]. Scopolamine, now available both in patch and tablet form, has also historically been used safely in pregnancy [174]. It has anticholinergic activity similar to atropine, and side effects such as blurred vision and dry mouth may make it less appealing. Also, if used near term it may cause fetal heart rate abnormalities that can be confusing during labour [175].

Topical insect repellents

Despite some early concerns with the use of insect repellents during pregnancy [176], controlled studies have been reassuring on this matter, at least in regard to the ingredient N,N-diethyl-M-toluamide (DEET) [177, 178]. It has been shown to cross the placental barrier in some studies and not in others; thus pregnant women should avoid the use of highly concentrated DEET-containing repellents. Animal studies of the newer agent icaridin have shown no adverse reproductive effects even at toxic levels [179]. No data from human experience are yet available. The safety and efficacy of other preparations has not been established and cannot be relied on to prevent malaria in endemic areas.

Permethrin, a synthetic pyrethroid, is not so much a repellent as a topical insecticide. It has not been found to be fetotoxic, mutagenic or teratogenic in bacteria or animals and there are no reports of harm from this agent in human pregnancies [180].

Malaria and pregnancy

Malaria during pregnancy raises grave concerns for a number of reasons.

Pregnant women appear to be more attractive to mosquitoes and therefore more at risk for malaria [181]. The mechanisms underlying this attraction may be related to increased exhalation of attractive substances, increased skin temperature or even an increased number of nocturnal trips to urinate.

Also, pregnant women have an increased susceptibility to *Plasmodium falciparum* infection. This increase appears to be greater during the first pregnancy and to diminish with subsequent pregnancies [182–186].

They are not only more likely to get malaria, the disease may be more difficult to diagnose due to sequestration of the parasites in the placenta, and its severity may be much greater than in the non-pregnant state. Malaria in pregnancy will often be characterised by very heavy parasitaemia, severe anaemia and sometimes profound hypoglycaemia, and may be complicated by cerebral malaria and pulmonary oedema. Placental sequestration of parasites often results in fetal loss due to abruption, premature labour and miscarriage. The infant born to the infected mother is more likely to be of low birth weight and to suffer from dehydration, seizures, thrombocytopenia and splenic rupture, and although rare, congenital malaria is a concern [187–189].

When possible, the pregnant traveller should be advised to avoid travel to *P. falciparum*-endemic areas. When such travel cannot be avoided, she should use all available protective measures including bed nets, being indoors from dusk until dawn, air-conditioned accommodations or window screens when possible, protective clothing, and the use of insecticides and insect repellents.

Plasmodium vivax infection

Plasmodium vivax is common in many parts of the tropics outside Africa. The effects of *P. vivax* have not been as well characterised. In a study in Thailand, *P. vivax* malaria was not associated with miscarriage, stillbirth or with a shortened duration of pregnancy, but it was associated with maternal anaemia and low birth weight. Also, congenital malaria is more common with *P. vivax* than with *P. falciparum*. Thus, antimalarial prophylaxis against *P. vivax* in pregnancy is still justified [190].

The safety of antimalarial drugs in general during pregnancy

Philips-Howard and Wood in a review of antimalarial use in pregnancy pointed out that none of the currently used antimalarials other than tetracycline have any demonstrated teratogenic effect [191]. Primaquine use is not recommended in pregnancy because of the inability to test the infant for G6PD deficiency and thus risk of haemolytic anaemia. Other than these precautions, the use of mefloquine, chloroquine-proguanil, pyrimethamine-sulfadoxine and atovaquone-proguanil have not shown any increase in adverse pregnancy outcomes when used in the first trimester of pregnancy. Treatment doses of quinine do not increase the risk of abortion or pre-term delivery, therapeutic mefloquine does not provoke hypoglycaemia, and there is no evidence to support the hypothetical risk of kernicterus in the newborn following exposure to antimalarial drugs containing sulfonamides or sulfones. Safety data regarding halofantrine and the artemisinin derivatives, accumulating slowly, still show no cause for alarm in these areas.

Chemoprophylaxis

A list of the available antimalarials and their uses and contraindications during pregnancy can be found in Table 25.10. Most travel health advisers recommend that pregnant women do not travel to areas where choloroquine-resistant

malaria occurs. However, sometimes a woman must travel to an endemic area and it is important to help a woman decrease that risk if travel is unavoidable. To do so, one must obtain up-to-date information regarding both the degree of risk and the available preventive measures. Which prophylactic medication to use should be determined by the resistance patterns and not simply an established safety profile in pregnancy. A safe but ineffective medication will be worse than no medication at all.

Chloroquine This has a long and well-established safety profile and certainly will be the drug of choice in areas where it is still effective [192, 193]. Levels of this drug in the umbilical cord at birth indicate ready passage of this agent to the fetus [194].

Mefloquine There now is extensive data to show mefloquine's safety in the second or third trimesters of pregnancy when used as prophylaxis [195–198]. There is some data to show that the pharmacokinetics of mefloquine in pregnancy result in lower blood levels so higher doses may be needed to provide prophylaxis [199]. Mefloquine should be used with caution in pregnancy and a careful travel health risk assessment is required when considering its use. As *P. falciparum* malaria during pregnancy can be severe, mefloquine may be considered for use in the first trimester of pregnancy in chloroquine-resistant areas.

Atovaquone/Proguanil (A/P) This has been used in treatment doses in some small populations with no evidence of pregnancy complications or fetal harm [200, 201]. Some reassurance may also be found in data from the use of the individual components. Atovaquone in animal studies has been shown to enter the fetal circulation but no fetal harm was seen when at concentrations two to three times those used in humans. Proguanil has a long history of safe use in pregnancy and in animal studies [202, 203], but in most areas is no longer effective when used by itself.

Pharmacokinetic studies of A/P used in treatment doses, however, showed a more rapid turnover of drug with diminished blood levels, perhaps indicating the need to use higher doses than in the non-pregnant state [204].

Doxycycline Doxycycline is not usually recommended for use in pregnancy because of the known adverse fetal effects of the related drug, tetracycline. These include damage to developing fetal bones and teeth. These effects have not been noted, however, in observations of doxycycline [205], and since dentition does not begin until about the seventeenth week of gestation, although US and UK guidelines advise against its use, some other advisories do include this medication for use at least during the first trimester of pregnancy.[206]

Primaquine Often used for terminal prophylaxis, this should not be given to a pregnant traveller because of the possibility of haemolytic anaemia in the fetus if the fetus is glucose-6-phosphate dehydrogenase (G6PD) deficient. Instead, weekly chloroquine or another appropriate antimalarial agent should be continued until delivery.

Chloroquine with proguanil Another option in some areas is a combination of weekly chloroquine and the proguanil daily. The main concern is resistance to biguanides and choloroquine.

Pyrimethamine with sulfadoxine (Fansidar) Pyrimethamine with sulfadoxine (Fansidar) has been recommended by WHO at any stage of pregnancy. It is also recommended for stand-by treatment while awaiting diagnosis. Concerns about this drug in pregnancy were the teratogenic effects of pyrimethamine in rats, preventable by folate supplementation, and hyperbilirubinaemia and kernicterus in the newborn due to sulfadoxine near term. In 1984 a series of severe cutaneous reactions were reported, thus limiting its use in the US. Resistance to Fansidar is increasing in many areas, further limiting its use.

Pyrimethamine and dapsone (Maloprim) Another combination is pyrimethamine in a fixed dose with dapsone and marketed as Maloprim. Pyrimethamine has raised concerns about teratogenicity in animal studies and haemolytic anaemia in humans [207]. Dapsone has been established as safe during pregnancy in leprosy patients. Although not recommended as a first-line drug, it may be considered for travellers to high-risk areas.

Amodiaquine Amodiaquine is considered safe for chemoprophylaxis in pregnant women, but increasing drug resistance precludes its use as a primary drug [208].

Quinine and Quinidine Stillbirths and congenital malformations have been described with the use of these drugs, as have neonatal thrombocytopenia and haemolytic anaemia in G6PD-deficient newborns. These quinine derivatives are used for life-threatening illness in pregnant women but they are not recommended for prophylaxis.

Artemisinin (qinghaosu) This drug and its derivatives belong to the endoperoxide class of antimalarials. They are potent blood schizonticides that rapidly reduce the parasitaemia but are not useful for prophylaxis due to their short half-life.

Co-administration of folate Regimens that include proguanil or pyrimethamine rely on a disruption of folate metabolism for their antimalarial action. Folate is an essential nutrient during pregnancy and is instrumental in preventing neural tube defects. Folate supplementation (up to 5 mg/day) is advised, therefore, in pregnant women who take these regimens. This supplementation has been shown to not interfere with the antimalarial effectiveness of the regimen [209].

Malaria prophylaxis when attempting to conceive

The question often arises as to whether it is safe for a woman to conceive while taking malaria prophylaxis, or how long she should wait to conceive after taking these medications.

The circulating half-life of chloroquine is approximately 10 days and it may remain in the circulation for up to 56 days, and mefloquine has a similar or longer duration. Atovaquone, proguanil and doxycycline, on the other hand, have half-lives in the 15- to 60-hour range. If a woman is to be entirely free of drug before conceiving, therefore, she should wait approximately 2 weeks after taking the shorter-acting drugs and as much as 3 months after the others.

Chloroquine and proguanil have a demonstrated safety profile in pregnancy, and there is an increasing body of evidence to support the use of mefloquine. As pointed out above, even though there are fewer data regarding atovaquone and doxycycline, they have not been shown to be detrimental in pregnancy. On the other hand, the dangers of malaria in pregnancy are well known. If there will be continued exposure to malaria, therefore, it would seem prudent to simply continue the prophylaxis.

Overall, the best course of action would appear to be to inform the patient of both the known risks of malaria and the theoretical risks of the medication and allow her to participate in the decision.

Multidrug-resistant falciparum malaria

Travel by pregnant women to an area with multidrug-resistant falciparum malaria should be avoided if possible. Some such areas are the Thai–Burma and Thai–Cambodia borders. Doxycycline is the drug of choice, but may be contraindicated in pregnancy (see above). If travel is unavoidable, the combination of sulfisoxasole and proguanil can be considered for prophylaxis in the second and third trimesters; however, the effectiveness of this drug combination is much less than that of doxycycline.

Malaria treatment

Any pregnant traveller with a fever who has travelled from an endemic area should be treated as an emergency. As mentioned above, malaria is not only more severe in pregnancy and has more dire consequences, it may also be more difficult to diagnose. Sequestration of parasites in the placenta may make peripheral blood smears less accurate. In addition, rapid decompensation with severe hypoglycaemia or other complications may occur. For these reasons, inpatient treatment with careful ongoing observation is usually recommended. Because the field of malaria treatment is rapidly changing, the travel health adviser and the pregnant women should contact one of the malaria centres to seek recommendations for treatment of malaria acquired at a particular destination (CDC, WHO, London School of Tropical Medicine, etc.).

Treatment for chloroquine-sensitive malaria is chloroquine. For severely ill pregnant travellers with life-threatening disease, intravenous quinine or quinidine gluconate is the drug of choice. Hypoglycaemia must watched for and prevented. Although not first line, mefloquine may be given for treatment as might Malarone.

For chloroquine-resistant malaria, treatment must be individualised according to the travel itinerary, the drug sensitivity pattern in the areas visited and the balance of the adverse effects of combinations of antimalarial drugs. The combination of atovaquone and proguanil achieves consistently high cure rates in adult patients with *P. falciparum* infection [210].

Stand-by treatment

Stand-by treatment is the self-administration of antimalarials when fever or 'flu-like' symptoms occur and prompt medical attention is not available. It is generally not recommended because inappropriate use may expose the mother and child to significant drug toxicity while also delaying appropriate diagnosis and treatment. In some situations, however, such treatment may be appropriate, depending on the traveller's knowledge of malaria and available resources. As the self-diagnostic tests become more reliable they will aid in this process. As prompt treatment is vital in the pregnant patient, self-administration of treatment doses of mefloquine or Malarone might be appropriate while en route to a treatment facility.

Breast-feeding while travelling

Women who will be breast-feeding while travelling also require special care.

The travel medicine provider is most likely to think of the medical issues involved, namely vaccines and medications. Chen *et al.* in their review of this subject point out the complexities involved in calculating drug transfer into breast milk – factors such as molecular weight, lipid solubility and

Table 25.12 The pregnant traveller medical kit

Equipment	Comfort items
Adhesive bandages	Talcum
BP cuff	Water
Stethoscope	Snack foods
Thermometer	Support stockings
Urine dipsticks	**Medications**
Symptom relief	Antibiotic cream
Acetaminophen	Antiemetic
Antiacid/antigas	Antimalarial
Antidiarrhoeal	Folic acid supplement
Bulk laxative	Antibiotic(s) for diarrhoea, urinary infection, respiratory infection, rupture of membranes, vaginitis
Cough/throat lozenges	Oral rehydration salt packets
Decongestant nasal spray	Prenatal vitamins
Haemorrhoidal cream	Vaginitis cream or tablet for monilial
Sunscreen	Methergonavine tablets in case of miscarriage

protein binding [211]. For instance, the higher the percentage of protein binding of the drug, the less will be available for transfer to the infant, while lipid soluble drugs would be expected to pass more readily into breast milk.

Once the drug does enter the breast milk in whatever amount, its effect on the infant will be further modulated by the frequency and volume of breast-feeding, bioavailability from the infant's intestine and a host of other factors. In general, however, it would appear that few commonly used medications would pass to the infant in sufficient amount to be either harmful or helpful, and the infant will need to be treated medically as a separate patient.

Specific medications that have raised concern in the past have been the tetracyclines (including doxycycline) and the quinolone antibiotics. The amount of drug passed to the infant in this manner, however, is small enough that these antibiotics are felt safe to use, at least for short periods such as 2–3 weeks [212].

In relation to malaria prophylaxis, chloroquine is felt to be safe in this circumstance, as are Malarone and mefloquine. Malarone is not prescribed for infants weighing less than 5 kg, however, so mothers whose infants weigh less than this may wish to avoid this drug. Also, when mefloquine is used the infant should be observed for signs of neuropsychiatric alterations and the medication discontinued if these occur. Primaquine should not be used unless the G6PD status of both mother and infant are known [213, 214].

Overall, however, the theoretical risk of the medication should be balanced against the risk of disease and the benefit to the infant of breast-feeding.

Similarly with vaccines, questions arise as to their safety and efficacy in relation to both mother and child. There are few data regarding the maternal immune status during breast-feeding, but it is generally felt that, unlike pregnancy, breast-feeding is not an immune-modulated state and thus there is little reason to expect any alteration of the efficacy of the vaccine in the mother. Whether the antibodies thus produced with be protective to the breast-fed infant or, on the other hand, interfere with subsequent immunisation of the child will vary depending on the vaccine. There is evidence, however, of viruses from live vaccines being passed to the breast-fed infant, sometimes with harm, but the available evidence supports the administration of rubella and varicella vaccines to nursing mothers [215–217]. Breast milk does not appear to alter the efficacy of vaccines administered to the infant [218, 219].

The patient, meanwhile, may be more concerned with the practical and cultural issues involved. Can she find the solitude and rest that successful breast-feeding may require? Will she need to pump her breasts and if so, how will she store the milk?

One factor that it is important for the provider to point out is the maintenance of adequate maternal hydration, especially if she travels to high altitude or suffers from diarrhoea. Cleanliness of the hands, breasts and all equipment is vitally important to prevent either mastitis or infant diarrhoea. Even the avoidance of mosquito bites when getting up at night to feed may need to be emphasised. As for cultural differences and norms, it may be encouraging to the patient to realise that she may, by successful breast-feeding, serve as a good role model in areas of the world where the practice is being largely abandoned to the detriment of infants.

Cultural and safety issues

Physical attacks and violence are not often addressed in the travel medicine literature but the WHO estimates that between 20 and 50% of women in the world have been physically or sexually assaulted at some point in their lives.

As some such assaults seem to be triggered by violation of local cultural norms, it is particularly important to find out as much as possible about the roles of both women and men in the places women plan to visit. Women should be prepared for the potential of sexual harassment and intimidation and know how to avoid or defuse such situations.

As a rule, they should avoid wearing provocative, form-fitting clothing. They should learn basic self-defence techniques, travel with minimal luggage and have an arm free. In

some cultures, it is considered incorrect for a woman to travel alone, or if she goes out at night on her own it means that she is 'available'. An excellent review of these issues may be found in *Her Own Way – Advice for the Woman Traveler* available from the Canadian department of Foreign Affairs and International Trade.

Conclusion

Travel medicine advisers should be able to address the key travel health issues for women across the lifespan during the pre-travel assessment. Pre-travel advice should include information on contraception, emergency contraception and prevention of sexually transmitted disease. The woman traveller's itinerary should be carefully evaluated for exposure to any travel or tropical disease that might have long-term consequences. There is a need for appreciation of gender-related issues in travel and tropical medicine and a need for further research.

References

1. Nelson AL (1998) Menstrual problems and common gynecological concerns. In: Hatcher RA *et al.* (eds) *Contraceptive Technology*, pp. 95–140. Ardent Media, New York.
2. Guillebaud J (2000) Reducing withdrawal bleeds. *Lancet* **355**(9221): 2168–2169.
3. Thomas SL and Ellertson C (2000) Nuisance or natural and healthy: should monthly menstruation be optional for women? *Lancet* **355**(9207): 922–924.
4. Nash HA *et al.* (1999) Estradiol-delivering vaginal rings for hormone replacement therapy. *Am J Obstet Gynecol* **181**(6): 1400–1406.
5. Gass M and Rebar R (2000) Hormone replacement for the new millennium. *Obstet Gynecol Clin North Am* **27**(3): 611–623.
6. Rioux JE *et al.* (2000) 17beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis. *Menopause* **7**(3): 156–161.
7. Hawkes S and Hart G (1998) The sexual health of travelers. *Infect Dis Clin North Am* **12**(2): 413–430.
8. Pinkerton SD *et al.* (1998) Cost-effectiveness of post-exposure prophylaxis following sexual exposure to HIV. *AIDS* **12**(9): 1067–1078.
9. Gerberding JL and Katz MH (1999) Post-exposure prophylaxis for HIV. *Adv Exp Med Biol* **458**: 213–222.
10. Guillebaud J (ed.) (2009) *Contraception: Your Questions Answered*, 5th edn. Elsevier, London.
11. Hatcher RA *et al.* (eds) (2009) *Contraceptive Technology*, 19th edn. Ardent Media, New York.
12. Weaver K and Glasier A (1999) Interaction between broad-spectrum antibiotics and the combined oral contraceptive pill. A literature review. *Contraception* **59**(2): 71–78.
13. Helms SE *et al.* (1997) Oral contraceptive failure rates and oral antibiotics. *J Am Acad Dermatol* **36**(5 Pt 1): 705–710.
14. Nelson A (2007) Combined oral contraceptives. In: Hatcher RA *et al.* (eds)*Contraceptive Technology*, 19th edn, p. 237. Ardent Media, Inc., New York.
15. Glasier A (1997) Emergency postcoital contraception. *N Engl J Med* **337**(15): 1058–1064.
16. Farmer RD *et al.* (2000) A comparison of the risks of venous thromboembolic disease in association with different combined oral contraceptives. *Br J Clin Pharmacol* **49**(6): 580–590.
17. Daly E *et al.* (1996) Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* **348**(9033): 977–980.
18. Oger E and Scarabin PY (1999) Assessment of the risk for venous thromboembolism among users of hormone replacement therapy. *Drugs Aging* **14**(1): 55–61.
19. Grady D *et al.* (2000) Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* **132**(9): 689–696.
20. Vandenbroucke JP *et al.* (2001) Oral contraceptives and the risk of venous thrombosis. *N Engl J Med* **344**(20): 1527–1535.
21. Schlagenhauf P *et al.* (2010) Sex and gender differences in travel-associated disease. *Clin Infect Dis* **50**(6): 826–832.
22. Vlassoff C (1997) The gender and tropical diseases task force of TDR: achievements and challenges. *Acta Trop* **67**(3): 173–180.
23. Hammill HA (1989) Unusual causes of vaginitis (excluding trichomonas, bacterial vaginosis, and Candida albicans). *Obstet Gynecol Clin North Am* **16**(2): 337–345.
24. Sloan BS *et al.* (1996) Schistosomiasis masquerading as carcinoma of the breast. *South Med J* **89**(3): 345–347.
25. Perez JA *et al.* (1997) Breast hydatid cyst. A case report. *Rev Med Chil* **125**(1): 66–70.
26. Goverde AJ *et al.* (1996) An unexpected guest in follicular fluid. *Hum Reprod* **11**(3): 531–532.
27. Balasch J *et al.* (1995) Schistosomiasis: an unusual cause of tubal infertility. *Hum Reprod* **10**(7): 1725–1727.
28. Stray-Pedersen B (2000) Parasitic infections. In: Wayne RCM and Sheldon H (eds) *Cherry and Merkatz's Complications of Pregnancy*, 5th edn, pp. 693–833. Lippincott, Williams and Wilkins, Philadelphia.
29. de Silva N *et al.* (1997) Anthelmintics. A comparative review of their clinical pharmacology. *Drugs* **53**(5): 769–788.
30. de Silva NR *et al.* (1999) Effect of mebendazole therapy during pregnancy on birth outcome. *Lancet* **353**(9159): 1145–1149.
31. REPROTOX® (2010) Diethylcarbamazine. Bethesda, MD: Reproductive Toxicology Center, http://www.reprotox.org (accessed 16 February 2010).
32. Fraser PJ (1972) Diethylcarbamazine: lack of teratogenic and abortifacient action in rats and rabbits. *Indian J Med Res* **60**(10): 1529–1532.
33. Pacque M *et al.* (1990) Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet* **336**(8729): 1486–1489.
34. Olds GR (2003) Administration of praziquantel to pregnant and lactating women. *Acta Trop* **86**(2–3): 185–195.
35. Cetron MS *et al.* (1996) Schistosomiasis in Lake Malawi. *Lancet* **348**(9037): 1274–1278.

36. Poggensee G *et al.* (2000) Screening of Tanzanian women of childbearing age for urinary schistosomiasis: validity of urine reagent strip readings and self-reported symptoms. *Bull World Health Organ* **78**(4): 542–548.
37. Feldmeier H *et al.* (1995) Female genital schistosomiasis. New challenges from a gender perspective. *Trop Geogr Med* **47**(2 Suppl.): S2–S15.
38. Feldmeier H *et al.* (1995) Female genital schistosomiasis: a neglected risk factor for the transmission of HIV? *Trans Roy Soc Trop Med Hyg* **89**(2): 237.
39. Poggensee G *et al.* (1999) Schistosomiasis of the female genital tract: public health aspects. *Parasitol Today* **15**(9): 378–381.
40. Li E and Stanley SL Jr (1996) Protozoa. Amebiasis. *Gastroenterol Clin North Am* **25**(3): 471–492.
41. Gilson GJ *et al.* (1995) Chagas disease in pregnancy. *Obstet Gynecol* **86**(4 Pt 2): 646–647.
42. Sinha A *et al.* (1999) African trypanosomiasis in two travelers from the United States. *Clin Infect Dis* **29**(4): 840–844.
43. Morgan DJ *et al.* (2007) Cutaneous leishmaniasis during pregnancy: exuberant lesions and potential fetal complications. *Clin Infect Dis* **45**(4): 478–482.
44. Figueiro-Filho EA *et al.* (2008) Visceral leishmaniasis and pregnancy: analysis of cases reported in a central-western region of Brazil. *Arch Gynecol Obstet* **278**(1): 13–16.
45. Meinecke CK *et al.* (1999) Congenital transmission of visceral leishmaniasis (Kala Azar) from an asymptomatic mother to her child. *Pediatrics* **104**(5): e65.
46. Topno RK *et al.* (2008) Visceral leishmaniasis in pregnancy – the role of amphotericin B. *Ann Trop Med Parasitol* **102**(3): 267–270.
47. American College of Obstetricians and Gynecologists (2001) Air Travel During Pregnancy. ACOG Committee Opinion #264, December 2001. PO Box 96920, Washington, DC 20090-6920.
48. Carter S (1999) Overview of common obstetric bleeding disorders. *Nurse Pract* **24**(3): 50–51, 54, 57–58 passim.
49. American College of Obstetricians and Gynecologists (1999 Prevention of Rh D Alloimmunization. ACOG Practice Bulletin #4. May, 1999. PO Box 96920, Washington, DC 20090-6920.
50. American College of Obstetricians and Gynecologists (2003) Management of Preterm Labor. ACOG Practice Bulletin #43, May 2003. PO Box 96920, Washington, DC 20090-6920.
51. American College of Obstetricians and Gynecologists (1998) Premature Rupture of Membranes. ACOG Practice Bulletin #1. June, 1998. PO Box 96920, Washington, DC 20090-6920.
52. Bia FJ (1992) Medical considerations for the pregnant traveler. *Infect Dis Clin North Am* **6**(2): 371–388.
53. Nicholas JS *et al.* (2000) Galactic cosmic radiation exposure of pregnant flight crewmembers. *Aviat Space Environ Med* **71**(6): 647–648.
54. Everson GT (1992) Gastrointestinal motility in pregnancy. *Gastroenterol Clin North Am* **21**(4): 751–776.
55. Agnew CL *et al.* (1993) Maternal/fetal dehydration: prolonged effects and responses to oral rehydration. *Am J Physiol* **264**(1 Pt 2): R197–R203.
56. Meyer A *et al.* (1997) Lethal maternal sepsis caused by Campylobacter jejunei: pathogen preserved in placenta and identified by molecular methods. *Mod Pathol* **10**(12): 1253–1256.
57. Simor AE and Farro S (1990) Campylobacter jejunei infection occurring during pregnancy. *Eur J Clin Microbiol Infect Dis* **9**(2): 142–144.
58. Goodyer L and Behrens RH (2000) Safety of iodine based water sterilization for travelers. *J Travel Med* **7**(1): 38.
59. Crepin G *et al.* (1978) Danger of iodine drugs in the pregnant woman [in French]. *Phlebologie* **31**: 279–285.
60. Einarson A *et al.* (2000) Prospective, controlled, multicentre study of loperamide in pregnancy. *Can J Gastroenterol* **14**(3): 185–187.
61. Gattuso JM and Kamm MA (1994) Adverse effects of drugs used in the management of constipation and diarrhoea. *Drug Saf* **10**(1): 47–65.
62. Quereux C *et al.* (1976) [Bismuth encephalopathy in pregnant women. Apropos of a case]. *J Gynecol Obstet Biol Reprod* **5**(1): 97–103. [Article in French].
63. Loebstein R *et al.* (1998) Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother* **42**(6): 1336–1339.
64. Larsen H *et al.* (2001) Birth outcome following maternal use of fluoroquinolones. *Int J Antimicrob Agents* **18**(3): 259–262.
65. Dupont HL *et al.* (2005) A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. *Ann Intern Med* **142**(10): 805–812.
66. Bertoli D and Borelli G (1984) [Teratogenic action of rifaximin in the rat and rabbit and its effect on perinatal development in the rat]. *Boll Soc Ital Biol Sper* **60** 1079–1085.
67. Bruel H *et al.* (1999) [Neutropenia in a newborn secondary to sulfamethoxazole-trimethoprim administered to the mother]. *Arch Pediatr* **6**(1): 107–108. [Article in French].
68. Allen SJ *et al.* (2004) Probiotics for treating infectious diarrhoea. *Cochrane Database Syst Rev* (2), CD003048.
69. Jaiswal SP *et al.* (2001) Viral hepatitis during pregnancy. *Int J Gynaecol Obstet* **72**(2): 103–108.
70. American College of Obstetricians and Gynecologists (1998) ACOG Educational Bulletin, No. 248, July 1998 – Viral Hepatitis in Pregnancy. American College of Obstetricians & Gynecologists, Washington, D.C.
71. Reinus JF *et al.* (1992) Failure to detect vertical transmission of hepatitis C virus. *Ann Intern Med* **117**(11): 881–886.
72. Abioye AA (1973) Fatal amoebic colitis in pregnancy and puerperium: a new clinico-pathological entity. *J Trop Med Hyg* **76**(4): 97–100.
73. Ravdin JI (1995) Amebiasis. *Clin Infect Dis* **20**(6): 1453–1464; quiz 65–66.
74. Bialek R and Knobloch J (1999) [Parasitic infections in pregnancy and congenital protozoan infections. Part I.: protozoan infections]. *Z Geburtshilfe Neonatol* **203**(2): 55–62.
75. Siegrist D and Siegrist-Obimpeh P (1992) Schistosoma haematobium infection in pregnancy. *Acta Trop* **50**(4): 317–321.
76. Smith JL (1999) Foodborne infections during pregnancy. *J Food Prot* **62**(7): 818–829.
77. American College of Obstetricians and Gynecologists (2000) ACOG Practice Bulletin, Number 20, September 2000 – Perinatal Viral and Parasitic Infections. American College of Obstetricians & Gynecologists, Washington, D.C.
78. Tan KS and Thomson NC (2000) Asthma in pregnancy. *Am J Med* **109**(9): 727–733.

79. Vaha-Eskeli KK *et al.* (1991) Haemodynamic response to moderate thermal stress in pregnancy. *Ann Med* **23**(2): 121–126.
80. Rao DL *et al.* (1995) Heat stroke – a probable cause of multiple fetal anomalies. *Indian J Pediatr* **62**(4): 493–495.
81. Hackett P (2001) High altitude and common medical conditions. In: Hornbein T and Schoene R (eds) *High Altitude: An Exploration of Human Adaptation*, p. 839. Dekker, New York, NY.
82. Jensen GM and Moore LG (1997) The effect of high altitude and other risk factors on birthweight: independent or interactive effects? *Am J Public Health* **87**(6): 1003–1007.
83. Niermeyer S (1999) The pregnant altitude visitor. *Adv Exp Med Biol* **474**: 65–77.
84. Katz VL *et al.* (1989) Pseudotumor cerebri and pregnancy. *Am J Perinatol* **6**(4): 442–445.
85. Nakatsuka T *et al.* (1992) Axial skeletal malformations induced by acetazolamide in rabbits. *Teratology* **45**(6): 629–636.
86. Scott WJ *et al.* (1981) Comparative studies on acetazolamide teratogenesis in pregnant rats, rabbits, and rhesus monkeys. *Teratology* **24**(1): 37–42.
87. Merlob P *et al.* (1990) Possible association between acetazolamide administration during pregnancy and metabolic disorders in the newborn. *Eur J Obstet Gynecol Reprod Biol* **35**(1): 85–88.
88. Artal R *et al.* (1995) A comparison of cardiopulmonary adaptations to exercise in pregnancy at sea level and altitude. *Am J Obstet Gynecol* **172**(4 Pt 1): 1170–1178; discussion 8–80.
89. American College of Obstetricians and Gynecologists (2002) ACOG Committee Opinion No. 267, January 2002 – Exercise During Pregnancy and the Postpartum Period. American College of Obstetricians & Gynecologists, Washington, D.C.
90. Clapp JF 3rd (2000) Exercise during pregnancy. A clinical update. *Clin Sports Med* **19**(2): 273–286.
91. Morton DC (1970) Gynaecological complications of water-skiing. *Med J Aust* **1**(25): 1256–1257.
92. Camporesi EM (1996) Diving and pregnancy. *Semin Perinatol* **20**(4): 292–302.
93. Morales M *et al.* (1999) [Pregnancy and scuba diving: what precautions?] *J Gynecol Obstet Biol Reprod* **28**(2): 118–123.
94. Henderson SO and Mallon WK (1998) Trauma in pregnancy. *Emerg Med Clin North Am* **16(1):** 209–228.
95. Pedler SJ (2000) Bacterial, fungal and parasitic infections. In: Barron WM and Davison JM (eds) *Medical Disorders During Pregnancy*, pp. 411–465. Mosby, St. Louis.
96. Luppi P (2003) How immune mechanisms are affected by pregnancy. *Vaccine* **21**(24): 3352–3357.
97. American College of Obstetricians and Gynecologists (2003) Immunization During Pregnancy. ACOG Committee Opinion #282. January, 2003. PO Box 96920, Washington, DC 20090-6920.
98. Anon (2007) Guidelines for Vaccinating Pregnant Women from Recommendations of the Advisory Committee on Immunization Practices (ACIP) October 1998 (Updated May 2007). Centers for Disease Control.
99. Munoz FM and Englund JA (2000) A step ahead. Infant protection through maternal immunization. *Pediatr Clin North Am* **47**(2): 449–463.
100. Brent RL (2006) Risks and benefits of immunizing pregnant women: the risk of doing nothing. *Reprod Toxicol* **21**(4): 383–389.
101. Fischer GW *et al.* (1997) Prospects for vaccines during pregnancy and in the newborn period. *Clin Perinatol* **24**(1): 231–249.
102. Demicheli V *et al.* (2005) Vaccines for women to prevent neonatal tetanus. *Cochrane Database Syst Rev* (4), CD002959.
103. Ogburn T *et al.* (2007) Impact of clinical interventions on the rate of influenza vaccination in pregnant women. *J Reprod Med* **52**(9): 753–756.
104. Nasidi A (1993) Yellow fever vaccination and pregnancy: a four-year prospective study. *Trans Roy Soc Trop Med Hyg* **87**(3): 337–339.
105. Grosheide PM *et al.* (1993) Immune response to hepatitis B vaccine in pregnant women receiving post-exposure prophylaxis. *Eur J Obstet Gynecol Reprod Biol* **50**(1): 53–58.
106. Fryauff DJ *et al.* (1998) Humoral immune response to tetanus-diphtheria vaccine given during extended use of chloroquine or primaquine malaria chemoprophylaxis. *J Infect Dis* **177**(6): 1762–1765.
107. Czeizel AE and Rockenbauer M (1999) Tetanus toxoid and congenital abnormalities. *Int J Gynaecol Obstet* **64**(3): 253–258.
108. Kalaca S *et al.* (2004) Missed opportunities for tetanus vaccination in pregnant women, and factors associated with seropositivity. *Public Health* **118**(5): 377–382.
109. MacLean DW and Calder MA (1981) Pertussis in pregnancy. *Scot Med J* **26**(3): 250–253.
110. Beiter A *et al.* (1993) Unrecognized maternal peripartum pertussis with subsequent fatal neonatal pertussis. *Obstet Gynecol* **82**(4 Pt 2 Suppl.): 691–693.
111. Mooi FR and de Greeff SC (2007) The case for maternal vaccination against pertussis. *Lancet Infect Dis* **7**(9): 614–624.
112. Anon (2000) CDC targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR: Morbid Mortal Wkly Rep* **49**: RR-6.
113. Ramsey PS and Ramin KD (2001) Pneumonia in pregnancy. *Obstet Gynecol Clin North Am* **28**(3): 553–569.
114. Glezen WP and Alpers M (1999) Maternal immunization. *Clin Infect Dis* **28**(2): 219–224.
115. Anon (1994) CDC typhoid immunization: recommendations of the Immunizations Practices Advisory Committee (ACIP). *MMWR: Morbid Mortal Wkly Rep* **43**: RR-14.
116. Mazzone T *et al.* (1994) Oral typhoid vaccine and pregnancy. *Reprod Toxicol* **8**(3): 278–280.
117. Urganci N *et al.* (2003) Neonatal cholestasis resulting from vertical transmission of hepatitis A infection. *Pediatr Infect Dis J* **22**(4): 381–382.
118. Elinav E *et al.* (2006) Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor. *Gastroenterology* **130**(4): 1129–1134.
119. Reinus JF and Leikin EL (1999) Viral hepatitis in pregnancy. *Clin Liver Dis* **3**(1): 116–130.
120. del Canho R *et al.* (1997) Ten-year neonatal hepatitis B vaccination program, The Netherlands, 1982–1992: protective efficacy and long-term immunogenicity. *Vaccine* **15**(15): 1624–1630.
121. Silverman NS and Greif A (2001) Influenza vaccination during pregnancy. Patients' and physicians' attitudes. *J Reprod Med* **46**(11): 989–994.
122. Yeager DP *et al.* (1999) Influenza vaccination in pregnancy. *Am J Perinatol* **16**(6): 283–286.

123. Anon (2004) ACOG Committee Opinion #305. Influenza vaccination and treatment during pregnancy. *Obstet Gynecol* **104**: 1125–1126.
124. Heinonen OP *et al.* (1977) *Birth Defects and Drugs in Pregnancy*. John Wright Publishing Sciences Group Inc., Littleton, MA, pp. 314–319, 473–474, 486–487.
125. Linder N *et al.* (1994) Effect of maternal immunization with oral poliovirus vaccine on neonatal immunity. *Pediatr Infect Dis J* **13**: 959–962.
126. Tulinius S and Zachau-Christiansen S (1964) Le probleme des malformations congenitales apres administration du vaccin peroral vivant polio type I aux femmes enceintes de mains de trois mois. *Med Hyg* **22**: 1075.
127. Ornoy A and Ben Ishai P (1993) Congenital anomalies after oral poliovirus vaccination during pregnancy. *Lancet* **341**(8853): 1162.
128. Chaturvedi US *et al.* (1980) Transplacental infection with Japanese encephalitis virus. *J Infect Dis* **141**: 712–715.
129. Fischer M *et al.* (2010) Japanese encephalitis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR: Morbid Mortal Wkly Rep* **59**(RR-1): 1–27.
130. Chutivongse S *et al.* (1995) Postexposure rabies vaccination during pregnancy: effect on 202 women and their infants. *Clin Infect Dis* **20**: 818–820.
131. Spence MR *et al.* (1975) Rabies exposure during pregnancy. *Am J Obstet Gynecol* **123**(6): 655–656.
132. Varner MW *et al.* (1982) Rabies vaccination in pregnancy. *Am J Obstet Gynecol* **143**(6): 717–718.
133. Miller EH and Wysocki S (2007) Vaccines in women. *Forum* **5**(2): 9–15.
134. Merck Pregnancy Registries (2011) Background Report on Exposure during Pregnancy from the Merck Pregnancy Registry for Gardasil. Merck & Company, North Wales PA, December 2006, http://www.merckpregnancyregistries.com (accessed 27 May 2012).
135. WHO Initiative for Vaccine Research (IVR) Vector-borne viral infections, Japanese encephalitis, http://www.who.int/vaccine_research/diseases/vector/en/index2.html (accessed 27 May 2012).
136. Schwartz HA (1950) Mumps in pregnancy. *Am J Obstet Gynecol* **60**(40): 875–876.
137. Ylinen O and Jarvinen PA (1953) Parotitis during pregnancy. *Acta Obstet Gynecol Scand* **32**(1): 121–128.
138. Greenberg MW and Beilly JS (1949) Congenital defects in the infant following mumps during pregnancy. *Am J Obstet Gynecol* **57**(4): 805–806.
139. Holowach J *et al.* (1957) Congenital defects in infants following mumps during pregnancy: a review of the literature and a report of chorioretinitis due to fetal infection. *J Pediatr* **50**(6): 689–694.
140. Aaby P *et al.* (1988) Increased perinatal mortality among children of mother's exposed to measles during pregnancy. *Lancet* **1**(8584): 516–519.
141. Chiba ME *et al.* (2003) Measles infection in pregnancy. *J Infect* **47**(1): 40–44.
142. De Santis M *et al.* (2006) Rubella infection in pregnancy. *Reprod Toxicol* **21**(4): 390–398.
143. CDC (2001) Notice to readers: revised ACIP recommendations for avoiding pregnancy after receiving a rubella containing vaccine. *MMWR: Morbid Mortal Wkly Rep* **50**(49): 1117.
144. Badilla X *et al.* (2007) Fetal risk associated with rubella vaccination during pregnancy. *Pediatr Infect Dis J* **26**(9): 830–835.
145. Bar-Oz B *et al.* (2004) Pregnancy outcome following rubella vaccination: a prospective controlled study. *Am J Med Genet* **130A**(1): 52–54.
146. Tan MP and Koren G (2006) Chickenpox in pregnancy: revisited. *Reprod Toxicol* **21**(4): 410–420.
147. Shields KE *et al.* (2001) Varicella vaccine exposure during pregnancy: data from the first 5 years of the pregnancy registry. *Obstet Gynecol* **98**: 14–19.
148. Robert E (1999) Exposure to yellow fever vaccine in early pregnancy. *Vaccine* **17**(3): 283–285.
149. Nishioka Sde A (1998) Yellow fever vaccination during pregnancy and spontaneous abortion: a case-control study. *Trop Med Int Health* **3**(1): 29–33.
150. Tsai TF *et al.* (1993) Congenital yellow fever virus infection after immunization in pregnancy. *J Infect Dis* **168**(6): 1520–1523.
151. Nasidi A *et al.* (1993) Yellow fever vaccination and pregnancy: a four-year prospective study. *Trans Roy Soc Trop Med Hyg* **87**(3): 337–339.
152. Suzano CE *et al.* (2006) The Campinas group on yellow fever immunization during pregnancy. The effects of yellow fever immunization (17DD) inadvertently used in early pregnancy during a mass campaign in Brazil. *Vaccine* **24**(9): 1421–1426.
153. Laibl VR and Sheffield JS (2005) Tuberculosis in pregnancy. *Clin Perinatol* **32**(3): 739–747.
154. Pranevicius A *et al.* (2003) [Course of pregnancy, delivery and newborn status in case of maternal tuberculosis][Article in Lithuanian]. *Medicina (Kaunas)* **39**(4): 399–402.
155. Tripathy SN and Tripathy SN (2003) Tuberculosis and pregnancy. *Int J Gynaecol Obstet* **80**(3): 247–253.
156. Diop SA *et al.* (2007) [Cholera and pregnancy: epidemiological, clinical, and evolutionary aspects.][Article in French]. *Med Mal Infect* **37**(12): 1816–1820.
157. Hill DR *et al.* (2007) Oral cholera vaccines: use in clinical practice. *Lancet Infect Dis* **7**(3): 176–178; author reply 178.
158. Ross L (1995) Congenital anomalies in two infants born after gestational gamma-globulin prophylaxis. *Acta Paediatr* **84**(12): 1436–1437.
159. Hayakawa F *et al.* (2002) Life-threatening human parvovirus B19 infection transmitted by intravenous immune globulin. *Br J Haematol* **118**(4): 1187–1189.
160. Koren G *et al.* (2002) Serum concentrations, efficacy, and safety of a new, intravenously administered varicella zoster immune globulin in pregnant women. *J Clin Pharmacol* **42**(3): 267–274.
161. Kadanali A *et al.* (2003) Anthrax during pregnancy: case reports and review. *Clin Infect Dis* **36**(10): 1343–1346.
162. Wiesen AR and Little CT (2002) Relationship between prepregnancy anthrax vaccination and pregnancy and birth outcomes among US Army women. *JAMA: J Am Med Assoc* **287**: 1556–1560.

163. ACOG (2002) Committee on Obstetric Practice, Management of asymptomatic pregnant or lactating women exposed to anthrax. *Int J Gynaecol Obstet* **77**(3): 293–295.
164. Green DM *et al.* (1966) Generalized vaccinia in the human fetus. *Lancet* **1**: 1296–1298.
165. Khan MY *et al.* (2001) Brucellosis in pregnant women. *Clin Infect Dis* **32**(8): 1172–1177.
166. WHO Initiative for Vaccine Research (IVR) Vector-borne viral infections, Overview http://www.who.int/vaccine_research/diseases/vector/en/index.html (accessed 29 May 2012).
167. Personal communication, Hoffman S. Sanaria Inc.
168. Aggarwal R and Jameel S (2008) Hepatitis E vaccine. *Hepatol Int* **2**(3): 308–315.
169. Briggs GG *et al.* (eds) (2008) *Drugs in Pregnancy and Lactation*, 8th edn' Lippincott, Williams & Wilkins, Philadelphia.
170. Parker CR Jr *et al.* (2000) Umbilical cord serum levels of thromboxane B2 in term infants of women who participated in a placebo-controlled trial of low-dose aspirin. *J Matern Fetal Med* **9**(4): 209–215.
171. Heyborne KD (2000) Preeclampsia prevention: lessons from the low-dose aspirin therapy trials. *Am J Obstet Gynecol* **183**(3): 523–528.
172. Baldwin GS (2000) Do NSAIDs contribute to acute fatty liver of pregnancy? *Med Hypotheses* **54**(5): 846–849.
173. Kallen B and Mottet I (2003) Delivery outcome after the use of meclozine in early pregnancy. *Eur J Epidemiol* **18**: 665–669.
174. Heinonen OP and Slone D (1977) *Birth Defects and Drugs in Pregnancy*. Publishing Sciences Group, Littleton, Massacheusets, pp. 346–353.
175. Ayromlooi J *et al.* (1980) The effects of scopolamine and ancillary analgesics upon the fetal heart rate recording. *J Reprod Med* **25**(6): 323–326.
176. Schaefer C and Peters PW (1992) Intrauterine diethyltoluamide exposure and fetal outcome. *Reprod Toxicol* **6**(2): 175–176.
177. McGready R *et al.* (2001) Safety of the insect repellent N,N-diethyl-M-toluamide (DEET) in pregnancy. *Am J Trop Med Hyg* **65**(4): 285–289.
178. McGready R *et al.* (2001) A double-blind randomized therapeutic trial of insect repellents for the prevention of malaria in pregnancy. *Trans Roy Soc Trop Med Hyg* **95**(2): 137–138.
179. Astroff AB *et al.* (1999) The conduct of a two-generation reproductive toxicity study via dermal exposure in the Sprague-Dawley rat – a case study with KBR 3023 (a prospective insect repellent). *Reprod Toxicol* **13**(3): 223–232.
180. Miyamoto J (1976) Degradation, metabolism and toxicity of synthetic pyrethroids. *Environ Health Perspect* **14**: 15–28.
181. Ansell J *et al.* (2002) Short-range attractiveness of pregnant women to Anopheles gambiae mosquitoes. *Trans Roy Soc Trop Med Hyg* **96**(2): 113–116.
182. Rietveld AEC (2001) 9.5 Special Groups: Pregnant Women, Infants, and Young Children Rietveld AE. Malaria prevention for special groups: pregnant women, infants and young children. In: Schlagenhauf P (ed.) *Travelers's Malaria*, pp. 303–323. BC Decker Inc, Hamilton.
183. Gilles HM (2002) Clinical features of malaria in pregnancy and children. In: Warrell DA and Gilles HM (eds) *Essential Malariology,* 4th edn, pp. 206–235. Arnold, London.
184. Nosten F *et al.* (1999) Effects of *Plasmodium vivax* malaria in pregnancy. *Lancet* **354**(9178): 546–549.
185. Desai M *et al.* (2007) Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis* **7**: 93–104.
186. Alecrim WD *et al.* (2000) *Plasmodium falciparum* infection in the pregnant patient. *Infect Dis Clin North Am* **14**(1): 83–95.
187. Diagne N *et al.* (2000) Increased susceptibility to malaria during the early postpartum period. *N Engl J Med* **343**(9): 598–603.
188. Duffy PE and Fried M (1999) Malaria during pregnancy: parasites, antibodies and chondroitin sulphate A. *Biochem Soc Trans* **27**(4): 478–482.
189. Steketee RW *et al.* (1996) The effect of malaria and malaria prevention in pregnancy on offspring birthweight, prematurity, and intrauterine growth retardation in rural Malawi. *Am J Trop Med Hyg* **55**(1 Suppl.): 33–41.
190. Nathwani D *et al.* (1992) *Plasmodium falciparum* malaria in pregnancy: a review. *Br J Obstet Gynaecol* **99**(2): 118–121.
191. Phillips-Howard PA and Wood D (1996) The safety of antimalarial drugs in pregnancy. *Drug Saf* **14**(3): 131–145.
192. Wolfe MS and Cordero JF (1985) Safety of chloroquine in chemosuppression of malaria during pregnancy. *Br Med J (Clin Res Ed)* **290**(6480): 1466–1467.
193. Nyirjesy P *et al.* (1993) Malaria during pregnancy: neonatal morbidity and mortality and the efficacy of chloroquine chemoprophylaxis. *Clin Infect Dis* **16**(1): 127–132.
194. Akintonwa A (1988) Placental and milk transfer of chloroquine in humans. *Ther Drug Monit* **10**(2): 147–149.
195. Nosten F *et al.* (1999) The effects of mefloquine treatment in pregnancy. *Clin Infect Dis* **28**(4): 808–815.
196. Phillips-Howard PA *et al.* (1998) Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy. *J Travel Med* **5**(3): 121–126.
197. Vanhauwere B *et al.* (1998) Post-marketing surveillance of prophylactic mefloquine (Lariam) use in pregnancy. *Am J Trop Med Hyg* **58**(1): 17–21.
198. Smoak BL *et al.* (1997) The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen. *J Infect Dis* **176**(3): 831–833.
199. Na Bangchang K *et al.* (1994) Mefloquine pharmacokinetics in pregnant women with acute falciparum malaria. *Trans Roy Soc Trop Med Hyg* **88**(3): 321–323.
200. McGready R *et al.* (2005) A Randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy. *J Infect Dis* **192**: 846–853.
201. McGready R *et al.* (2003) Artesunate-atovaquone-proguanil rescue treatment of multidrug-resistant *Plasmodium falciparum* malaria in pregnancy: a preliminary report. *Trans Roy Soc Trop Med Hyg* **97**(5): 592–594.
202. Anonymous (1983) Pyrimethamine combinations in pregnancy. *Lancet* **2**(8357): 1005–1007.

203. Landauer W (1978) Cholinomimetic teratogens. VI. The interaction of cholinomimetic teratogens with the antimalarial drugs chloroquine and chlorguanide. *Teratology* **17**(3): 335–340.
204. Na-Bangchang K *et al.* (2005) The pharmacokinetics and pharmacodynamics of atovaquoe and proguanil for the treatment of uncomplicated falciparum malaria in third-trimester pregnant women. *Eur J Clin Pharmacol* **61**(8): 573–582.
205. Kazy Z *et al.* (2007) Effect of doxycycline treatment during pregnancy for birth outcomes. *Reprod Toxicol* **24**(3–4): 279–280. Epub 2007 Aug 7.
206. Chiodini P *et al.* (2007) Guidelines for malaria prevention in travelers from the United Kingdom. London, Health Protection Agency, January 2007.
207. Luzzi GA and Peto TEA (1993) Adverse effects of antimalarials. An update. *Drug Saf* **8**: 295–311.
208. Tagbor H *et al.* (2006) Efficacy, safety, and tolerability of amodiaquine plus sulphadoxine-pyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial. *Lancet* **368**: 1349–1356.
209. Mbaye A *et al.* (2006) Lack of inhibition of the anti-malarial action of sulfadoxine-pyrimethamine by folic acid supplementation when used for intermittent preventive treatment in Gambian primigravidae. *Am J Trop Med Hyg* **74**(6): 960–964.
210. McGready R *et al.* (2003) The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. *Eur J Clin Pharmacol* **59**(7): 545–552. Epub 2003 Aug 30.
211. Chen LH *et al.* (2010) Breastfeeding travelers: precautions and recommendations. *J Travel Med* **17**(1): 32–47.
212. Anon (2001) Update: interim recommendations for antimicrobial prophylaxis for children and breastfeeding mothers and treatment of children with anthrax. *MMWR: Morbid Mortal Wkly Rep* **50**(45): 1014–1016.
213. CDC (2007) Health Information for International Travel. US Department of Health and Human Services, Public Health Service, Atlanta, GA.
214. Hale T (2008) *Medications and Mother's Milk*, 8th edn. Hale Publishing, L.P., Amarillo.
215. Cono J *et al.* (2003) Smallpox vaccination and adverse reactions. Guidance for clinicians. *MMWR: Morbid Mortal Wkly Rep* **52** (RR-4): 1–28.
216. Losonsky GA *et al.* (1982) Effect of immunization against rubella on lactation products. II. Maternal-neonatal interactions. *J Infect Dis* **145**(5): 661–666.
217. Bohlke K *et al.* (2003) Postpartum varicella vaccination: is the vaccine virus excreted in breast milk? *Obstet Gynecol* **102**(5 Pt 1): 970–977.
218. Kim-Farley R *et al.* (1982) Vaccination and breast feeding. *JAMA: J Am Med Assoc* **248**(19): 2451–2452.
219. Krogh V *et al.* (1989) Postpartum immunization with rubella virus vaccine and antibody response in breast-feeding infants. *J Lab Clin Med* **113**(6): 695–699.
220. Carroll ID and Williams DC (2008) Pre-travel vaccination and medical prophylaxis in the pregnant traveler. *Travel Med Infect Dis* **6**(5): 259–275.

Chapter 26 The immunocompromised traveller

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Introduction

Several issues need to be considered in travellers who are immunocompromised, depending on the type of immunological disorder. In general, immunocompromised travellers are at a higher risk of a number of infectious diseases associated with travel. These include infection with measles, influenza, varicella zoster virus, human papilloma virus, hepatitis B virus, mycobacterium tuberculosis and pneumococcal disease. The association between infection with malaria and asplenia is well known, but remains anecdotal. There is no evidence that other tropical infectious diseases are associated with severe infection in asplenic travellers [1]. On the other hand, immunocompromised travellers may have a decreased immunological response to vaccines compared with the immunologically healthy traveller. Serological testing for the presence of antibodies is therefore indicated following some vaccinations, notably following vaccination against hepatitis A, hepatitis B, rubella, tick-borne encephalitis (TBE) and rabies. This is not required as a matter of routine practice for most of the other travel-related vaccines. Measurable correlates of protection are not clearly established for pertussis or *Haemophilus influenzae B* (Hib), for example. Further, the administration of live attenuated vaccines is contraindicated in certain immunocompromised travellers and indeed, some additional vaccinations may need to be considered. Absolute compliance with a course of malaria prophylaxis alongside strict adherence to bite avoidance measures might also be indicated. A prescription of antibiotics as prophylaxis or stand-by treatment should be considered to prevent certain tropical infections and avoidance of certain risk behaviour should also be discussed. Drug-induced immunocompromised travellers make up by far the largest group and the list of these drugs has increased considerably over recent years with the introduction of the biological products.

Basic pre-travel advice that applies to all travellers is covered elsewhere in this book and will not be considered in this chapter. It is advisable for any traveller with a specific medical problem to carry a medical alert card or disc summarising their medical history, underlying condition and current treatment. In the case of a complex medical problem, the traveller will benefit from carrying a copy of their latest medical report. Entry to a foreign country while carrying drugs for a specific medical condition during travel warrants a 'To whom it may concern' note from the attending physician. In most western countries, lists of recognised clinics are available to give to the traveller so that they may seek advice at the most appropriate institution in case of emergencies. For instance, lists are available for diabetic and dialysis clinics. The International Society of Travel Medicine also provides lists with the addresses of clinics run by their members. Travellers should be made aware that this information is available to them before travel [2].

The following categories of immunocompromised travellers may be recognised:

- non-HIV-related immune deficiencies
- HIV-related immune deficiency
- the pregnant traveller (*see* Chapter 25).

NON-HIV-RELATED IMMUNODEFICIENCIES

Travellers with non-HIV-related immunodeficiencies can be subdivided for practical purposes into three categories.

- The traveller with an underlying chronic disease, such as diabetes mellitus, chronic cardiovascular disease, chronic pulmonary obstructive disease, chronic renal disease, including nephrotic syndrome, liver cirrhosis, alcoholism and to some extent the elderly whose immune system may not function as well. These will be discussed in Chapter 27.

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Table 26.1 The traveller with a congenital immunodeficiency

B-cell deficiency: common variable immunodeficiency (CVI), IgA deficiency, X-linked agammaglobulinemia
T-cell deficiency: severe combined immune deficiency (SCID), some with CVI also have T cell deficiency
Phagocytes deficiency: chronic granulomatous disease (CGD), cyclic neutropenia
Complement deficiencies
Congenital asplenia

Table 26.2 The traveller with acquired immunodeficiency

Malignancy: leukaemias, lymphomas, metastatic solid tumour disease
Autoimmune disease
Transplant patients
Splenectomy or functional hyposplenia
Drug-induced immune suppression

- The traveller with an underlying congenital immune deficiency due to a cellular or humoral immunodeficiency (Table 26.1).
- The traveller with an acquired immunodeficiency due to a splenectomy, malignancy, autoimmune disease or drug-induced immunosuppression. This category also includes those travellers with a solid organ or stem cell transplant (Table 26.2).

Congenital immunodeficiency due to a cellular or humoral immunodeficiency

Although this is a heterogeneous group of rare disorders, from time to time patients with one of these conditions will consider travelling and will require special consideration before travelling. Table 26.1 lists the conditions seen most frequently and some of these will be discussed here.

Severe combined immune deficiency (SCID) is a rare T cell disorder that usually presents within the first few months of life. In addition, B cell function is mostly compromised, leading to both cell-mediated and humoral deficiencies. Life expectancy will generally be short; however, if these patients reach an age at which they wish to travel, travel to countries that require the administration of live vaccines

Case history

A 56-year-old woman with type 1 diabetes went on a walking trip in the Andes with her husband, something they had done before in the Alps and the Pyrenees without experiencing any problems. Before her vacation she discussed her trip with her diabetes nurse. Hypo- and hyperglycaemia were discussed, glucagon was prescribed, she was advised how to travel with her medication, how to use her monitoring strips and pens, and she was given letters to be shown as necessary at customs and if she were to require any medical assistance while travelling. She was referred to the travel clinic for a travel health risk assessment tailored to meet her health needs. Her vaccinations for hepatitis A and B were still valid following a trip to South Africa 3 years earlier. She was also given travel health advice on several travel health issues, e.g. avoiding gastrointestinal infections, rabies, etc. Antibiotics in case of gastrointestinal infections, in particular travellers' diarrhoea, were also prescribed. She was advised to have yellow fever, a booster of diphtheria-tetanus-polio and parental typhoid vaccinations. She was advised to avoid travel to altitudes above 3,000 m because her concomitant medication includes diuretics and antidiabetic drugs and there are contraindications to the use of acetazolamide (Diamox). On the ninth day of their trip when they were at an altitude of 1,900 m, and after a good day's walk, they took shelter because of a thunderstorm. The traveller ate her last sandwich and drank some milk. It was well over 2.5 hours before they were able to continue their trek and as the guide was anxious that they might miss their pick-up, her husband hurried her along and refused her permission to stop to check her blood glucose level. Forty minutes after continuing their walk she felt dizzy and unsteady on the feet, and as her husband was preparing to take a blood glucose reading and had the glucagon ready she fell over and was unable to stand. Her blood glucose reading was 2.2 mmol/l. Her husband injected her with glucagon and she recovered slowly. However, she was still not able to stand because of severe pain in her right ankle, which had become swollen. She had to be taken to the main road by stretcher and on arrival at the hospital well over 3 hours later, was shown to have a fracture. Her blood glucose reading at that time was 3.7 mmol/l. She had an uneventful recovery and was even fortunate enough not to experience any gastrointestinal infections during the entire trip.

should be discouraged because of the possibility of disseminated or persistent infection following administration of live attenuated vaccines. This has been described following administration of BCG and oral polio vaccination, but the same can be expected following administration of oral typhoid vaccine and yellow fever vaccine.

B cell and humoral immunodeficiency present early, and with the rarely seen X-linked agammaglobulinaemia, this is usually before the age of 2 years. Other types of B cell and humoral immunodeficiency do not usually become clinically relevant until the third decade of life and the presenting infections are predominantly with encapsulated bacteria such as *pneumococci, meningococci* and *Haemophilus influenzae B*. Common variable immunodeficiency (CVI) and, to a lesser extent, IgA deficiency are a heterogeneous group of diseases that share the features of hypogammaglobulinaemia and include an increased susceptibility to chronic enteric infections with *Giardia lamblia, Campylobacter* spp and disseminated echo-viral infections, in addition to sinopulmonary bacterial infections. IgA also plays a role as an anti- adhesive agent for *Haemophilus influenzae B* and *meningococcal disease*. A person with one of these conditions travelling to less hygienic destinations need to be protected specifically by vaccination against *pneumococci*, common *meningococci* and *Haemophilus influenzae B*. Response to vaccination will usually be diminished or absent and ideally seroconversion should be checked. Special attention needs to be given to the prevention of infections such as typhoid fever as well as *Shigella, Salmonella, Campylobacter spp* and *Giardia lamblia* for which standby treatment is available. The immunodeficiency disorder due to insufficient phagocytosis, which is a rare life-threatening condition, will not be discussed here.

A problem with complement-mediated immunity is that the clinical presentation (with certain bacterial systemic infections) of the disease can present as late as in young adulthood and might be asymptomatic and therefore unknown to the traveller. The clinical picture depends on the type of complement that is deficient. For instance, late complement defects (C5–C9) are associated with recurrent *Neisseria* spp (bacteraemia and meningitis) and early complement pathway defects are associated with bacterial pneumonia. As soon as the complement defect presents clinically, these patients should be vaccinated against *Neisseria* spp or *pneumococci* spp. It is essential that these vaccinations be checked before travel. In addition, antibiotics should be prescribed as stand-by treatment in the event of the occurrence of a respiratory tract infection with fever [3].

Congenital asplenia and the implications for travel will be discussed in the next section.

Case history

A 24-year-old man came for advice before trekking through India and Nepal. He had an IgA deficiency, and had been treated on and off until the age of 18 by a paediatrician, mainly for respiratory tract infections, and had been plagued by chronic nasal congestion. In childhood he had received the usual vaccinations without problems. He received diphtheria-tetanus and polio boosters, typhoid fever vaccine, hepatitis A vaccine, quadrivalent meningococcal vaccine and Hib vaccine (as he had not received Hib vaccination in childhood). Instructions were given on the use of stand-by treatment with appropriate antibiotics for respiratory tract infections and bacterial gastrointestinal infections, and also on treatment for giardiasis, for which tinidazole was prescribed, a more convenient regimen compared with metronidazole in terms of duration and side effects. Advice on malaria prophylaxis was included. Several western countries have a rather restricted advice on the use of malaria prophylaxis, but this was not considered to a be problem in IgA deficiency. After 4 weeks in India he entered Nepal, where he developed watery diarrhoea, bloating of the abdomen and nausea. He suspected *Giardia lamblia* infection and according to his pre-travel instructions took tinidazole, 4 tablets of 500 mg once. He recovered over the succeeding days, but gradually developed intermittent diarrhoea with nausea and weight loss of 6 kg over 6 weeks. On return home he was diagnosed again with *G. lamblia* in his stool, but also *Plesiomonas shigelloides*, a bacterium more often found in immunocompromised patients. After adequate treatment he made a full recovery.

Acquired immunodeficiency

Table 26.2 shows a subdivision of different disorders belonging to the category of acquired immunodeficiency. Immunodeficiency as part of haematological malignancies can occur because of either T and/or B cell impairment. Splenectomy as a result of a diagnostic procedure or treatment of an underlying malignancy can also play a part in immunodeficiency, while the effect of ongoing or recent chemotherapy and the influence of haematopoietic stem cell transplantation (HSCT) should also be taken into account. Loss of B cell function occurs in chronic lymphocytic leukaemia (CLL) together with a loss of phagocyte function. Patients who have

undergone stem cell transplantation will show both B and T cell impairment [4]. These differences in the function of the immune system result commonly in different reactions to vaccination, and not all immunocompromised travellers are the same [5].

The best-studied vaccines administered to those with haematological diseases and malignancies are pneumococcal and influenza vaccines. In patients suffering from CLL, antibody response rates to vaccine antigens are lower compared with controls. However, if the vaccine is administered at an early stage of the disease, i.e. before the commencement of chemotherapy and the development of hypogammaglobulinaemia, a significant vaccination response to at least six pneumococcal antigens may be obtained in almost 40% of CLL patients [6]. There is limited evidence to demonstrate that an inferior response to hepatitis B vaccination in patients with haematological disease being treated with chemotherapy or shortly after chemotherapy can occur [7]. Those travellers with underlying haematological disease or who have had a splenectomy, should be vaccinated against hepatitis B and/or pneumococcal disease prior to travel as part of the travel health risk assessment. A course of booster dose of DTP is recommended similarly. Live vaccines are contraindicated while patients are receiving chemotherapy or are being treated for Host versus Graft disease and there are no available data on the effect of vaccination against typhoid fever, hepatitis A, rabies, cholera, Japanese encephalitis, TBE or tuberculosis either.

In general, HSTC patients are advised to abstain from travelling within 24 months after transplantation. After that period the incidence of Host versus Graft is unlikely as is the administration of prolonged use of immunosupressants; otherwise the limitations associated with these should be discussed. If travel during the high-risk period is unavoidable, it should be strictly discouraged during the first 3 months following transplantation when the risk of acquiring infectious disease is at its highest. For the period of 3 months up to 1 year post-transplantation, strict advice regarding food preparation should be given, especially the avoidance of undercooked meat and fish. Live attenuated vaccines are contraindicated within the first year following transplantation [8]. Inactivated vaccines may be administered more than 6 months after transplantation, although in general, a weaker antibody response is seen than with normal subjects [9].

Research has been undertaken to investigate the immunogenicity of vaccinations in patients who have undergone HSCT and no differences were found between those who had received an autologous or an allogenic transplant. Patients who had undergone HSCT were found to have a suboptimal response to pneumococcal polysaccharide vaccine (PPV23). Administration of a pneumococcal conjugate vaccine (PCV7) resulted in an enhanced immune response [10]. Vaccination against *Haemophilus influenzae B* in patients undergoing HSCT provides a reasonable level of protection. In a small group of patients who had undergone HSCT and had suffered from hepatitis B before HSCT, a course of hepatitis B vaccination post-transplantation proved to be successful in avoiding a reactivation of infection with hepatitis B [11,12]. Vaccination against hepatitis B in HSTC patients after discontinuation of chemotherapy showed a lower antibody response than in healthy vaccinated controls. The response was adversely influenced for those over the age of 18 years, while the type of HSTC, Graft versus Host disease and type of drug treatment after HSTC did not influence the response (a total of 64% of patients seroconverted) [13].

Asplenia

The spleen provides a multitude of important host defence functions. Surgical removal of the spleen, or splenic dysfunction because of disease, results in a heightened predisposition to sepsis caused by *pneumococci, H. influenzae, meningococci* and a variety of other encapsulated bacteria, such as *Capnocytophaga canimorsus* (after dog bites). Asplenia or hyposplenia also predisposes to severe infection with intraerythrocytic parasites such as *Plasmodium falciparum* and *Babesia microti*. The risk of acquiring these infections in these travellers is determined largely by the age at which the splenectomy was performed and the indication for splenectomy. If splenectomy is carried out above the age of 5 years, acquired immunity leads to reduced risk of acquiring an infectious disease. It has been suggested that in post-traumatic splenectomy, splenic cells adhere to the peritoneum and might partially take over splenic function, although there is no evidence for this hypothesis. However, the risk of post-splenectomy sepsis after splenectomy for splenic trauma appears to be lower than that found in patients who were splenectomised for other reasons, such as a haematological disorder (malignancy, idiopathic thrombocytopenia, hereditary spherocytosis, etc.). In general, after any splenectomy the risk of developing fulminant sepsis decreases after 2–3 years, but a lifelong increased risk of a serious course of certain infections will exist [14]. The same problem can be seen in the hypo-functional spleen, as occurs in sickle cell disease, thalassaemia, certain lymphoid malignancies and irradiated spleens. Before travel, travellers without a functioning spleen, or those who have undergone splenectomy, need to be protected sufficiently against encapsulated bacteria and malaria. Ideally, before splenectomy patients should have received pneumococcal vaccination, as the response to pneumococcal vaccine is reduced thereafter. Whether this also applies to other vaccinations is unknown.

As well as being provided with pre-travel health advice, these travellers should be given adequate vaccination coverage against *pneumococci, meningococci and H. influenzae B*.

Vaccination against pneumococcal infection after splenectomy studied in patients with splenectomy and haematological malignancies demonstrated a poor response to the 23-valent polysaccharide vaccine. Response to the conjugated *H. influenzae B* vaccine was slightly better, but still significantly lower than in individuals with post-traumatic splenectomy [15]. In another study, it was found that following a haematological disease, a substantial proportion of splenectomised patients mounted a poor antibody response and remained at risk of pneumococcal infections despite vaccination. In the absence of indirect clinical predictors of antibody response, with the exception of age, measurement of antibody levels seems to be a feasible method for early identification of this patient subgroup. Poor responders did not benefit from revaccination, and should be offered other prophylactic measures while travelling [16].

Malaria prophylaxis needs to be optimal, and stand-by treatment for malaria should be available in case of unexpected breakthrough infection. Travel to multiresistant *P. falciparum* areas without adequate medical facilities should be discouraged. The absolute necessity of using bite avoidance measures is self-evident. In case of fever with or without signs of a respiratory tract infection, adequate antibiotics to treat a possible *pneumococcal* infection in relation to the visited area should be prescribed and should be started promptly. A thick blood film to exclude malaria should be done without delay at the same time. Immediate prophylactic antibiotic treatment with co-amoxiclav (7 days) or, in cases of penicillin allergy, clindamycin (300 mg three times a day for 7 days) must be initiated following a bite by a dog or cat.

Other causes of acquired immunosuppression

Solid tumour disease is likely to lead to immunosuppression, depending on the type and measure of progressive disease. Pre-travel health advice is essential and should be considered with regard to the severity of the patient's condition using the Karnofski scale. The level of immune deficiency in these patients is often difficult to establish. When travel is considered in such patients, common sense should prevail. Solid organ transplant patients have a significant cellular immunity disfunction, with the intensity of the immunosuppression dictated by the type of organ that has been transplanted. The level of immunosuppression will be at its greatest up to 6 months after transplantation [17]. There have been four questionnaire-based studies on solid transplant recipients who have travelled. Of the 1,715 subjects in this category who travelled, 486 travelled outside of Europe or North America. There was a wide variation in the severity of their illness, the number of years after transplantation and the destinations visited. The incidence of diarrhoea varied from 7% to 44% of travellers, while respiratory tract infection varied from 16% to 70% [18–21]. In one study there were 17 travel-related illnesses in 59 subjects, which included 4 hospital admissions [18]. Two travellers experienced a graft rejection after making their preparations for travel [19, 20]. Vaccination is an important therapeutic approach to minimise the occurrence of infectious disease complications in organ transplant recipients, including when travelling. It is best to complete the administration of the appropriate vaccinations, including those required for any proposed travel, before transplantation takes place and this should be performed as early as possible in the course of the underlying disease. In current practice, however, the administration of pre-transplantation vaccinations is often not considered. Therefore the clinical practice of travel medicine involves a travel health risk assessment with an unvaccinated post-transplantation traveller. Prospective randomised studies on the efficacy of vaccines in transplant recipients are rare. Following transplantation, all inactivated vaccines may be safely administered to transplant recipients, whereas live attenuated vaccines are strictly contraindicated or should only be administered after a careful risk-benefit assessment. In this regard it is also important to know that there is no evidence linking graft rejection with post-transplant vaccination. As vaccine-specific protective immunity may wane more rapidly on initiation of immunosuppressive drug therapy, monitoring of specific immunity may help to identify patients who have lost protective immunity and may benefit from booster immunisations. Serological testing is not common practice, because as mentioned earlier, the interpretation and availability of serological tests is not standardised for most vaccines. When booster immunisations or primary vaccinations are administered after transplantation, increased efficacy is to be expected approximately 6 months post transplantation [22].

No interaction has been shown between oral prophylactic drugs prescribed to travellers for malaria and medication used to suppress rejection after solid organ transplantation, except that chloroquine, mefloquine, primaquine and doxycycline can increase the serum level of calcineurin inhibitors e.g. ciclosporin (Neoral, Sandimmune) and tacrolimus (Prograft) used at the same time; what the practical implications of this observation are, however, is not clear [23].

Drug-induced immunosuppression

The drugs responsible most frequently for immunosuppression are listed in Table 26.3. It should not be forgotten that these drugs are often prescribed in diseases where an inherent immunodeficiency is also present and also there is a clear

Case history

A 33-year-old Dutch man was repatriated after becoming seriously ill on a trip to Mozambique. He was transferred initially to Johannesburg, where he was found to have received adequate treatment for infection with falciparum malaria and he remained well on return to the Netherlands. At this point, a review of his malaria prophylaxis for Mozambique revealed that this had been inappropriate, especially in view of his past medical history of the successful treatment with mantle field radiotherapy of stage 2 Hodgkin's lymphoma some 12 years previously. The traveller had received a pneumococcal vaccination at that time but a booster dose had not been administered. No other vaccination history could be ascertained. The traveller denied knowledge of ever having been told he should be considered as potentially 'asplenic'. During the time at which he received pre-travel advice he was asked if his spleen had been removed and whether he was receiving treatment for any current serious disease; he explained that neither were the case. A pneumococcal booster vaccination, *Haemophilus influenza* B and meningococcal vaccination were administered and he was advised to seek advice from the travel clinic in advance of any future trips to malaria-endemic areas to ensure that he receives appropriate malaria chemoprophylaxis.

Table 26.3 Immunosuppressive and cytotoxic drugs

Glucocorticosteroids

>10 mg prednisone daily, for more than 2 weeks, or <10 mg prednisone daily but >700 mg totally in continuous use. (CDC: Low-dose, i.e. 20 mg or less of prednisone or equivalent/day, or short-term use [less than 2 weeks] are no problem)

Chemotherapeutic/Oncolytic agents

- Alkylating agents (busulfan, chlorambucil, cyclophosphamide, dacarbazine, estramustine, ifosfamide, lomustine, melfalan, procarbazine, tremozalamide, thiotepa)
- Antimetabolites (fluorouracil, methotrexate, mercaptopurine and tioguanine)
- Antimitotics (vinblastine, vincristine)
- Cytostatic antibiotics (bleomycine, doxyrubicine, mitomycine)
- Other oncolytic agents (etoposide, asparaginase, cis-platinum)

Immunomodulators

- Tumour necrosis factor alpha blocking agents (infliximab, adalimumab, etanercept, certolizumab, golimumab)
- Others: rituximab (anti CD20), anakinra (human interleukine-1 receptor antagonist), abatacept (anti T cell costimulation, CTLA4), tocilizumab (anti IL6 receptor), leflunomide, methotrexate, azathioprine, ciclosporin, tacrolimus, mycophenolate, mofetil.

Immunostimulators

e.g. interferon

difference between the different drugs in their level of immunosuppression. In general, alkylating agents and antimetabolites are considered to be mild in their impact on immune status when used in maintenance dose [24, 25]. On the other side of the spectrum a drug like rituximab can give rise to advice not to travel. The immunological changes caused by the underlying disease and the severity of the disease also influence serological conversion after vaccination.

The exact amount of systemic glucocorticosteroids and the duration of administration needed to suppress immunity are not known. Controlled randomised studies done in the late 1980s indicated that the rate of infectious complications in patients given a daily dose of less than 10 mg prednisone or a cumulative dose of less than 700 mg prednisone was not increased compared with that of controls [26]. Other studies indicate that even this might be too strict, and that 20 mg/day of prednisone could be sufficiently immunosuppressive to affect vaccination [1]. Most clinicians consider a dose of either >2 mg/kg of body weight or ≥20 mg/day of prednisone or equivalent in persons who weigh >10 kg, when administered for ≥2 weeks, as sufficiently immunosuppressive to raise concern about the safety of vaccination with live vaccines. Furthermore, the immune response to vaccines may be impaired. Vaccine providers should wait at least 1 month after discontinuation of high-dose systemically absorbed corticosteroid therapy before administering a live-virus vaccine (CDC Yellow Book 2010). Travellers receiving treatment with glucocorticosteroids should not receive live attenuated vaccines within 1 month following their last dose of glucocorticosteroids.

It is important to note that live vaccines may be administered as outlined below.

- Following treatment with glucocorticosteroids for 2 weeks or less
- Following replacement treatment with a physiological dose of glucocorticosteroids, i.e. 7.5 mg daily.
- Following the administration of glucocorticosteroids topically, by inhalation or by intra-articular, bursal or tendon local injection.

Haematological malignancies in general will lead to more immune suppression than solid organ tumours. In addition, most chemotherapeutic agents will make patients more

prone to certain opportunistic infections depending on the underlying condition and treatment. In general, it is most unlikely that these patients will plan to travel during their treatment. Travellers with haematological malignancies should not receive live attenuated vaccines within the first 3 months following treatment with chemotherapy or radiotherapy (UK guidance is within at least the last 6 months of treatment, Department of Health, UK. Immunisation against Infectious Disease). Travellers who have received a bone marrow transplant should not receive live attenuated vaccines until at least 12 months after finishing all immunosuppressive treatment. No data are available on the effect of solid organ malignancies and live attenuated vaccines, but the above advice also applies to this group of patients. The antibody response following administration of other vaccines during and in the first 3 months after treatment will be suboptimal [6].

Since the publication of the first edition of this book, a whole new group of medications, the biologicals, or immune modulators have become available. These have important consequences regarding the immune status of the traveller, much more so than drug-induced immunosuppression. One study reported that 14 out of 2,200 travellers visiting a travel clinic over a 2-month period who required yellow fever vaccination where found to be receiving treatment with immune-modulating drugs. Four of these patients were advised to change their itinerary and none of them had been aware that travel under these circumstances would pose a problem or risk to their health [27]. Therefore ideally, pre-travel health advice including vaccinations should be given early on in the course of disease and before immune-modulating therapy is started. On the other hand, a Brazilian study interviewed 70 travellers with rheumatoid disease 8 weeks following administration of yellow fever vaccination, and the percentage of those who experienced side effects was no higher than in a healthy population while they were being treated with various immune-modulating drugs and often combinations of these drugs. In another study, nine persons vaccinated while being treated with immune modulators did not experience any serious side effects [28]. The consequence of this is that these travellers require tailored pre-travel health advice. As a general rule, it is accepted that immune suppression caused by drugs continues for 3 months after the drugs are stopped, but this varies from probably less than 1 month for corticosteroids to perhaps 6 months for infliximab. With patients using them for a short period, the postponement of their travel should therefore be discussed. For all drugs, it is considered safe to restart medication a period of 3– 4 weeks after vaccination [29].

Live attenuated vaccines cannot be administered to patients receiving drugs that cause significant immunosuppression as these vaccines may induce disseminated infection. Therefore generally BCG, MMR, yellow fever, oral typhoid fever, oral poliomyelitis, varicella and rotavirus vaccines are contraindicated. Most studies investigating this were completed in patients with a history of haematological malignancy, who received vaccines against influenza and pneumococcal disease. The literature does not provide good data on the use of travel-related vaccines in any of these conditions. The use of live attenuated vaccines should therefore be administered with caution and expert advice. The second problem in administering these vaccines is the diminished immune response. In the presence of significant immunosuppression, serological tests should be carried out before and after vaccination with inactivated vaccines such as hepatitis A, hepatitis B, rabies and tick-borne encephalitis(TBE). With the exception of TBE, protection with specific immune globulin is possible when there has been a risk of infection, if seroconversion has not been achieved by vaccination. There is no evidence that patients receiving these immune modulators run a higher risk of contracting malaria [29, 30].

Drugs such as interferon and aldesleukine actually stimulate the immune system, but very few studies have been done to look at their effect on vaccination; however, the general opinion is that there is no reason to believe that they would decrease the immune response to vaccination and there is no formal contraindication to administering live vaccines in travellers using these drugs. However, as they can inhibit virus growth they could inhibit antibody formation following administration of live attenuated vaccines, and this has been shown in combination with drugs such as ribavarine [31].

Other biologicals work by blocking receptors within the immune system and therefore have clear implications for the development of an immune response and tolerance to vaccinations. In general, one can state that the biologicals that belong to the anti-tumour necrosis subgroup cause a diminished antibody response, but the preliminary data available for drugs such as rituximab and batacept suggest these agents have the ability to seriously blunt the immune responses to both infections and vaccinations, and live attenuated vaccines can not be given until 6 months after these drugs have been discontinued. Studies on the combination of immunosuppressant drugs in patients with rheumatoid arthritis show that this does not seriously undermine the response to antibody formation any further [30].

HIV-RELATED IMMUNE DEFICIENCY

Infection with the human immunodeficiency virus (HIV) causes a gradual decrease of CD4+ T lymphocytes. These cells have an important role within the human defence

Case history

A 54-year-old man, of Javanese background, is planning to make a trip home to see his elderly and ailing parents. At the age of 51 he underwent a liver transplant, for hepatitis B-induced cirrhosis in which a small hepatoma had developed. Since the transplant just over 3 years ago, he has been treated with mycophenolate mofetil (500 mg bd) and prednisolone (10 mg od). He is in good health with no signs of liver dysfunction. At the time of the transplant he received hepatitis B immunoglobulin and antiviral drugs. There was no evidence of recurring hepatitis B infection. At the time of transplantation he was found to be IgG positive for hepatitis A, and so after the transplantation, he received a full course of diphtheria, tetanus and poliomyelitis. Over the past 5 years, he has been vaccinated against influenza every autumn. His case was discussed with the transplant coordinator and it was decided that the main risk was from acquiring a gastrointestinal infection and except for typhoid vaccination, no further vaccination was indicated. The traveller received much advice regarding the avoidance of travellers' diarrhoea, including maintaining adequate food and water hygiene. He was further advised not to walk barefooted outside to avoid potential exposure to Strongyloides infection and the possibility of a subsequent hyperinfection with this roundworm. Stand-by antibiotics, including written instructions, were prescribed for the treatment of a serious gastrointestinal infection. Although he was planning to visit malaria-endemic regions in Indonesia, at the time ProMed warned of a dengue epidemic in Java, and so he was advised about the observance of mosquito bite avoidance measures in the daytime to minimise the risk of infection. His itinerary was such that he was not considered to be at risk of infection with Japanese encephalitis. Having had a very successful trip, he was seen 2 months later in the travel clinic with a skin rash, which was, in fact, not travel-related.

system and consequently, both the cellular and the humoral defence system are diminished, leading to increased vulnerability to opportunistic infections. A less-effective immune response to immunisation and an increased risk of complications after administration of live attenuated vaccines are also seen. In clinical practice, the number of CD4+ cells present in the peripheral blood is a measure of the level of immune suppression following infection with HIV. CD4+ counts above 500/mm^3 correspond to a normal immune status. Counts between 200 and 499/mm^3 indicate moderate immune suppression, while a CD4+ level below 200/mm^3 indicates severe suppression of the immune system. Whether this is the case in HIV patients is debatable, as a study on immune restoration in HIV-infected individuals treated with highly active antiretroviral therapy (HAART), resulting in a CD4(+) T cell count greater than 500 cells/μl, showed an incomplete recovery. However, the majority of HIV-infected individuals are capable of mounting a long-lasting immune response, including several pivotal T cell-dependent processes, following vaccination with a neoantigen such as the rabies vaccine [32]. The lower the CD4+ count, which correlates reciprocally with the amount of viral load, the greater the risk of acquiring opportunistic infections. What is not quite clear is whether it is the lowest CD4+ count ever reached or the count achieved after HAART therapy that is a determinate of the immune status. It is advisable therefore in the first few months after starting HAART therapy to also consider the number of CD4+ cells before initiating therapy. There are several issues of importance to consider when advising HIV-infected travellers:

- their increased vulnerability to infection
- the decreased efficacy of or contraindications to administration of vaccines
- the interaction of anti-HIV drugs with, most importantly, antimalarial prophylactic drugs
- the practical problems that may be encountered at the borders of many countries.

The availability of treatment in many parts of the world and corresponding insurance difficulties should also be considered carefully.

When HAART is taken, usually a combination of HIV reverse transcriptase(NRTI) and protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (nNRTI), viral replication is inhibited and the CD4+ level increases. Opportunistic infections are treated more easily and occur much less frequently, and consequently the quality of life returns and patients are much more likely to want to travel [33].

In every pre-travel health consultation with an HIV-infected traveller the following should be considered in order to ensure tailor-made advice is given to address their individual health needs.

- What degree of immune suppression is present?
- What are the risks of (tropical) infection during this particular journey?
- Which advice on hygiene is indicated?
- Which live attenuated vaccines are contraindicated?
- Which other vaccines should be recommended ?
- Is there a need to complete antibody tests after vaccination?
- Is there a need for stand-by antibiotic and other medication in case of diarrhoea, malaria or other health conditions?

• Is instruction needed for the time of administration of HAART when passing to other time zones?
• Is it necessary to consider interaction between HAART and prophylactic medication, including malaria chemoprophylaxis and stand-by treatment for malaria?
• Is there a need for medical check-ups to be undertaken during travel?

BCG, oral typhoid and oral polio vaccination are contraindicated in HIV travellers. Yellow fever vaccine should be administered with caution and only when the risk of exposure to yellow fever is considered significant and when the CD4+ count is greater than 200/mm^3. The immune response to polysaccharidetyphoid vaccine and polysaccharide pneumococcal vaccine is clearly related to the number of CD4+ cells, with reduced antibody formation and levels of protection when the CD4+ count falls below 200/mm^3. Above 500/mm^3 the antibody production achieved was comparable to healthy subjects [34]. HIV positive patients vaccinated at 0 and 24 weeks against hepatitis A showed that those with over 300/mm^3 CD4+ cells at 24 weeks had the same immune response as healthy subjects. If however the CD4+ count was less than 300/mm^3, 20% of the patients did not achieve levels of protection greater than 20 mIU/ml [35]. In another study comparing two doses versus three doses of hepatitis A vaccine, the percentage of patients achieving protection increased from 60 to 80% [36]. In patients with a low CD4+ count the immune response to rabies is diminished significantly, while the immune response to yellow fever vaccine is only slightly diminished. There have been reports regarding adverse effects following administration of yellow fever vaccination in patients being treated with Maraviroc as part of their HAART regime, caused by a blocking of the CCR5 receptor, and therefore yellow fever vaccine should not be administered under these circumstances [37].

Table 26.4 summarises the risk of infection, the use and side effects of vaccines and other advice necessary for HIV-infected travellers.

Table 26.4 Travel health considerations for pre- and post-travel advice for HIV-infected travellers

Degree of immunosuppression	CD4 count/mm^3	Infection risk	Vaccinations	Contraindication to vaccinations	Additional vaccinations	Additional travel health advice
Mild	>500	None	None	BCG	Pneumococci Influenza MMR	Diarrhoea: standard advice Tuberculosis[a]
Moderate	200–499	Pneumococci *Haemophilus influenzae* *Campylobacter jejuni* *Shigella* spp *Salmonella* (non-typhi) *Mycobacterium tuberculosis* Visceral leishmaniasis Measles	All vaccines Consider measuring antibody titres after hepatitis A/B, TBE and rabies vaccination	Oral typhoid fever Oral polio BCG Yellow fever MMR	As above	Diarrhoea >2 days blood or fever: antibiotics Tuberculosis[a]
Severe	<200	The above plus *Cryptosporidium* spp. *Isospora belli* *Giardia lamblia* *Histoplasma capsulatum* *Coccidioides immitis* Penicillium marneffi *Strongyloides* spp.	As above	As above	As above	Every episode of diarrhoea: antibiotics (consider prophylaxis) Tuberculosis[a]

TBE = tick-borne encephalitis, MMR = measles, mumps, rubella.
[a]Tuberculosis post-travel check-up is recommended for travellers who have travelled abroad for more than 6 weeks and/or have close contact with the local population.

HIV infection with a low CD4+ count is associated with increased parasitemia following infection with *Plasmodium falciparum*, but a more serious course of disease compared with immunocompetent individuals has never been established [38]. Adequate malaria chemoprophylaxis as with healthy travellers is advised, but potential interactions with drugs used in HAART should be carefully considered before departure [39], including some interactions with prophylactic drugs used to prevent opportunistic infections. A potential interaction of HAART combination treatment with proguanil and quinine should be considered, but insufficient data are currently available to determine whether this constitutes a significant problem. In travellers using a combination of nNRTIs and ritonavir, the serum level of atovaquone (Malarone) can be lowered but the clinical relevance of this interaction is as yet unknown. Mefloquine levels do not seem to be influenced by anti retroviral therapy [40]. HIV patients with a complicated anti-retroviral drug regimen should be referred to or discussed with a specialist travel medicine practitioner. If antiretroviral drugs do interact with malaria chemoprophylaxis, adjustment of the travel itinerary to non-malaria-endemic areas should be considered. Mefloquine and chloroquine should be used with caution in HIV travellers who have been treated for cerebral space-occupying lesions such as non-Hodgkin lymphoma and toxoplasmosis. In these cases mefloquine and chloroquine have the potential to induce seizures.

Particular attention should be given to the prevention of infection with enteropathogens, such as the parasites *G. lamblia, Cryptosporidium and Isospora bellïi*, and the bacteria *Campylobacter*, *Shigella and Salmonella*. Water and food hygiene are essential, and stand-by treatment for these pathogens can be prescribed for HIV-infected travellers with a severe or an intermediate degree of immune deficiency. Those with a severe or an intermediate degree of immune deficiency also have an increased risk of infection with tuberculosis, and prolonged close contact with the local population in tuberculosis-endemic areas should be avoided. Walking barefoot outside should also be discouraged because of the risk of acquiring *Strongyloides* infection.

Case history

A 45-year-old woman visited the travel clinic 3 weeks in advance of a trip to the Amazon region of Brazil. Her travel health record form stated that she was healthy and not receiving any treatment. Where she was asked on the travel health form which medication she is currently taking, she wrote a number of abbreviations which, on further questioning turned out to be HAART therapy as she was infected with HIV. One of the drugs she listed was Maraviroc and a review showed that she had a CD4 count of >500/mm^3 (this had never been <200/mm^3), and she did not have a measurable viral load. She had recently received influenza and pneumococcal vaccinations. She was given advice regarding yellow fever vaccination which is recommended for travel to the Amazon region, but contraindicated with the use of Maraviroc. She stated that she would travel to the Amazon region irrespective of the travel health advice given, despite the seriousness of infection with yellow fever having been explained. Antibody levels for hepatitis A and B were taken, as she had been fully vaccinated against Hepatitis B when she was found to be HIV seropositive. Boosters for diphtheria/tetanus/polio and typhoid were administered. Preventive protection measures against malaria and dengue, gastrointestinal infections, rabies and schistosomiasis were also discussed. When she returned for the results of her blood tests, she had cancelled the trip to Brazil and was now travelling to Nicaragua and Belize and was leaving in 10 days time. The blood results demonstrated no detectable antibodies against hepatitis A and B and so two doses of the combined hepatitis A and B vaccine were administered with a 7-day interval before she travelled. Malaria chemopophylaxis in the form of proguanil 200 mg od was dispensed, even though the risk of malaria was considered to be low. Upon return from an uneventful trip, the third dose of hepatitis A/B was given at 6 weeks. A further 6 weeks later, antibody levels for hepatitis A and B were found to be 1500 and 320 U/l respectively and a booster dose of the combined hepatitis A/B vaccine was recommended in 12 months time.

Summary

HIV-infected individuals with an adequately functioning immune system, including travellers being treated with less than 20 mg prednisone daily for more than 2 weeks, those on short courses (less than 2 weeks) of high-dose steroids, steroid inhalers and those who have received intra-articular steroid injections, are at no greater risk of infection than the traveller without an underlying health problem. Appropriate vaccines may be administered similarly. In general, before administering live vaccines, a period of 1 month should elapse following the discontinuation of high-dose steroids or severely immunosuppressive drugs. Individuals with haematological diseases in remission should wait 3 months after the last oncolytic drugs before receiving live virus vaccines. Individuals with less severe immune deficiency, such as chronic renal, hepatic or endocrine disease, should be counselled regarding the increased risk of acquiring various

infections; however, the appropriate pre-travel immunisations should be considered and administered. Functionally hyposplenic or asplenic travellers should be vaccinated against pneumococci, meningococci and *Haemophilus influenzae* type B, and influenza, if they have not already been already vaccinated. Specific attention and advice should also be considered for elderly travellers who may develop suboptimal responses to many travel-related vaccines and to the pregnant traveller who also falls under the group known as the 'immunocompromised traveller'. The travel health needs of these travellers are described in Chapter 25.

References

1. CDC Website, http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/yellow-fever.aspx (accessed 31 May 2012).
2. Murphy KM *et al.* (2007) *Janeway's Immunobiology: The Immune System in Health and Disease*, 7th edn. Garland Science Textbooks, London.
3. Sneller MC *et al.* (1993) The new insights into common variable immunodeficiency. *Ann Int Med* **118**: 720–730.
4. Sinisalo M *et al.* (2007) Antibody response to 7-valent conjugated pneumococcal vaccine in patients with chronic lymphocytic leukaemia. *Vaccine* **26**(1): 82–87.
5. Plotkin SA and Orenstein WA (2008) *Vaccines*, 5th edn. WB Saunders, Philadelphia.
6. Pirofski LA and Casadevall A (1998) Use of licensed vaccines for active immunisation of the immunocompromised host. *Clin Microbiol Rev* **11**: 954–963.
7. Pullukcu H *et al.* (2008) Efficacy of accelerated hepatitis B vaccination program in patients being actively treated for hematologic malignancies. *Int J Infect Dis* **12**(2): 166–170.
8. Dykewicz CA (2001) Summary of the guidelines for preventing opportunistic infections amongst hematopoietic stem cell transplant recipients. *Clin Infect Dis* **33**: 139–144.
9. Rolston KV and Wingard JR (2003) Managing infections in patients with hematologic malignancies. New York: Academy of healthcare Education; 1–22.
10. Kumar D *et al.* (2007) A randomized, double-blind trial of pneumococcal vaccination in adult allogeneic stem cell transplant donors and recipients. *Clin Infect Dis* **45**(12): 1576–1582.
11. Pao M *et al.* (2008) Response to pneumococcal (PNCRM7) and haemophilus influenzae conjugate vaccines (HIB) in pediatric and adult recipients of an allogeneic hematopoietic cell transplantation (alloHCT). *Biol Blood Marrow Transplant* **14**(9): 1022–1030.
12. Onozawa M *et al.* (2008) HB vaccination in the prevention of viral reactivation in allogeneic hematopoietic stem cell transplantation recipients with previous HBV infection. *Biol Blood Marrow Transplant* **14**(11): 1226–1230.
13. Jaffe D *et al.* (2006) Immunogenicity of recombinant hepatitis B vaccine (rHBV) in recipients of unrelated or related allogeneic hematopoietic cell (HC) transplants. *Blood* **108**(7): 2470–2475.
14. Lutwick L (2010) Infections in asplenic patients. In: Mandell GL *et al.* (eds) *Principles and Practice of Infectious Diseases*, 7th edn, pp. 3865–3873. Churchill-Livingstone-Elsevier, Philadelphia, PA.
15. Eigenberger K *et al.* (2007) Antibody responses to pneumococcal and hemophilus vaccinations in splenectomized patients with hematological malignancies or trauma. *Wiener Klinische Wochenschrift* **119**(7–8): 228–234.
16. Cherif H *et al.* (2006) Poor antibody response to pneumococcal polysaccharide vaccination suggests increased susceptibility to pneumococcal infection in splenectomized patients with hematological diseases. *Vaccine* **24**(1): 75–81.
17. Geissler EK and Schlitt HJ (2009) Immunosuppression for liver transplantation. *Gut* **58**(3): 452–463.
18. Roukens AH *et al.* (2007) Health preparations and travel-related morbidity of kidney transplant recipients travelling to developing countries. *Clin Transplant* **21**(4): 567–570.
19. Uslan DZ *et al.* (2008) International travel and exposure risks in solid-organ transplant recipients. *Transplantation* **86**(3): 407–412.
20. Boggild AK *et al.* (2004) Travel patterns and risk behaviour in solid organ transplant recipients. *J Travel Med* **11**(1): 37–43.
21. Kofidis T *et al.* (2002) Traveling after heart transplantation. *Clin Transplant* **16**(4): 280–284.
22. Sester M *et al.* (2008) Vaccination of the solid organ transplant recipient. *Transplant Rev* **22**: 274–284.
23. Kotton CN *et al.* (2005) Prevention of infection in adult travelers after solid organ transplantation. *Am J Transplant* **5**: 8–14.
24. Glück T and Müller-Ladner U (2008) Vaccination in patients with chronic rheumatic or autoimmune diseases. *Clin Infect Dis* **46**: 1459–1465.
25. O'Neill SG and Isenberg DA (2006) Immunizing patients with systemic lupus erythematosus: a review of effectiveness and safety. *Lupus* **15**(11): 778–783.
26. Stuck AE *et al.* (1989) Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis* **11**: 954–963.
27. Winkel K van de *et al.* (2007) Factors influencing standard pretravel health advice – a study in Belgium. *J Travel Med* **14**: 288–296.
28. Mota LM *et al.* (2009) Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases. *Revista da Sociedade Brasileira de Medicina Tropical* **42**(1): 23–27.
29. Rahier JF *et al.* (2009) European Evidence-Based Consensus on the prevention diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohn's Colitis* **3**(2): 47–91.
30. Brezinscheck HP *et al.* (2008) Immunization of patients with rheumatoid arthritis with antitumor necrosis factoralfa and methotrexate. *Curr Opin Rheumatol* **20**: 295–299.
31. Gelinck LBS *et al.* (2008) Praktische adviezen voor reizigers met een afweerstoornis. *Nederlands Tijdschrift voor Geneeskunde* **152**: 1725–1729. (Stand van zaken, Richtlijnen).
32. Gelinck LB *et al.* (2009) Restoration of the antibody response upon rabies vaccination in HIV-infected patients treated with HAART. *AIDS* **23**(18): 2451–2458.
33. Kroon FP (2008) Travelling with Haart. *Tijdschrift voor Infectieziekten*, 2008(3) **6**: 207–213.
34. Kroon FP (1999) Humoral immune response to vaccinations in HIV-infected individuals. Thesis, University of Leiden. The Netherlands.

35. Wallace MR *et al.* (2004) Safety and immunogenicity of an inactivated hepatitis A vaccine among HIV-infected subjects. *Clin Infect Dis* **39**(8): 1207–1213. Epub 2004 Sep 24.
36. Launay O *et al.* (2008) HEPAVAC Study Group1. Immunological efficacy of a three dose schedule of hepattis A vaccine in HIV Infected adulst: Hepavac Study. *J Acquired Immune Deficiency Syndromes (1999)* **49**(3): 272–275.
37. Roukens AH *et al.* (2009) A note of caution on yellow fever vaccination during maraviroc treatment: a hypothesis on a potential dangerous interaction. *AIDS* **23**(4): 542–543.
38. Laufer MK *et al.* (2006) Impact of HIV associated Immunosuppression on malaria infection and disease in Malawi. *J Infect Dis* **193**: 872–878.
39. Brunette GW (ed.) (2012) *CDC Health Information for International Travel*, Table 8.2: Potential interactions between malaria drugs and HIV drugs, p. 529. Oxford University Press, New York.
40. Schippers EF *et al.* (2000) No drug-drug interaction between nelfinavir or indinavir and mefloquine in HIV-1-infected patients. *AIDS* **14**(17): 2794–2795.

Chapter 27 High-risk travellers

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Introduction

More than ever before, the benefits of travel are readily accessible to persons with physical limitations of all varieties. Individuals with underlying medical conditions and physical disabilities often present challenging questions to primary care physicians and travel medicine experts regarding their potential travel risks. The elderly, chronically ill and those with physical disabilities account for an increasing number of the 800 million travellers who cross international boundaries each year.

Although pre-travel counselling usually emphasises the prevention of infectious and tropical diseases – and certainly these should be addressed in the elderly and high-risk travellers – it is important to realise that travellers rarely die from these illnesses. Fifty to 75% of deaths in travellers are due to natural causes, mainly cardiovascular disease [1–3]. Accidental death, most often due to motor vehicle accidents, drowning and homicides, is the second leading cause of mortality among travellers and occurs more frequently in younger age groups [1–3]. The elderly and other high-risk travellers may be at higher risk for car accidents and other injuries due to slower reaction times, visual and/or auditory impairments, gait difficulties and adverse effects of medications. At some travel destinations, Americans die primarily as a result of injury, and usually without ever reaching a hospital [4]. Even if transport to a hospital occurs, many will not have adequate trauma facilities and evacuation may be required.

Pre-travel advice for elderly travellers, even those in excellent health, and those with chronic medical conditions must therefore include risk reduction strategies for non-infectious health problems, as well as education regarding the management of the potential medical complications of travel. Morbidity and mortality from non-infectious health problems are increased in these travellers, even in those with no identifiable health problems before departure. Healthcare standards during travel may differ from those of industrialised nations. Illness or hospitalisation in foreign countries, where communication can be difficult, may be particularly stressful for the elderly, and stress can often be prevented with appropriate advice. Some simple but easily overlooked preparations prior to travel will eliminate unnecessary delays and contribute to a healthy, enjoyable travel experience. Issues surrounding travel risks for these special travellers, and focused advice for each group, will be addressed in this chapter. Travel advice and risks for immunocompromised individuals have been addressed in Chapter 26 and will not be included here.

General advice

A general medical check-up should be performed to assess any high-risk individual's fitness for vigorous, remote or prolonged travel, and to identify any unsuspected health problems that may prevent travel. Travellers with known underlying medical conditions should plan well in advance and consult with a travel medicine physician at least 6 weeks prior to departure. For individuals with serious medical conditions, especially those that may result in an altered level of consciousness, a medical bracelet can allow rapid identification of these problems and could be life saving.

There are few absolute medical contraindications to travel, and these are listed in Table 27.1. Some pre-existing illnesses may actually abate or improve with travel [5]. Many relative contraindications are remediable with time and/or appropriate medical therapy. Some specific considerations for travellers with underlying medical conditions include precautions every travel medicine expert should know, such as the contraindication to mefloquine use for persons with neuropsychiatric disorders, including seizures, and general avoidance of live vaccines in immunocompromised persons.

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Table 27.1 Medical contraindications to air travel

Absolute contraindications
Pneumothorax or pneumomediastinum within previous 3 weeks
Thoracic, cardiac, abdominal, middle ear surgery within previous 2 weeks
Acute myocardial infarction within 2 weeks if uncomplicated, or within 6 weeks if complicated
Uncontrolled angina, congestive heart failure or dysrhythmia within previous 2 weeks
Cerebrovascular infarction within 2 weeks
Relative contraindications[a]
Respiratory tract infection, including sinusitis, otitis, pneumonia
Cyanosis or dyspnoea at rest or with exercise
Active uncontrolled bronchospasm
Inadequate pulmonary function as indicated by one or more of the following:
– Vital capacity or diffusing capacity < 50% of predicted
– Hypercapnia (Pco_2 > 50 mmHg)
– Hypoxaemia (Po_2 < 50 mmHg on room air)
– Haemoglobin < 7.5 g/dl (75 g/l) or sickle cell anaemia

[a]Relative contraindications can usually be improved or corrected prior to travel.

Adapted from Sullivan and Jong (2003) Travel with chronic medical conditions. In: Jong EC, Sanford C (eds) The Travel and Tropical Medicine Manual, 4th edn, p. 257. Elsevier, London; and Barbeau DN (2010) Advising Travelers with Special Needs, CDC Health Information for International Travel 2010: The Yellow Book.

There is an absolute contraindication to hyoscine (scopolamine) use in persons with visual disorders such as glaucoma and retinal disease. Less well-known is that hyoscine use is contraindicated in persons with hypertrophy of the prostate gland, who may develop acute urinary retention. Thus a fairly complete medical history must be reviewed prior to making recommendations, even for those conditions that may seem benign to comment on and prescribe for, such as motion sickness.

If a significant increase in physical activity is expected during travel, a conditioning programme started 1 or 2 months before travel can increase cardiovascular fitness and muscular strength and identify potential limitations or problems. Exercise stress testing for asymptomatic individuals may be considered in men over 40 years of age and women over 50 who are beginning vigorous exercise, and for older travellers planning remote or lengthy treks, particularly those with a prior history of cardiac disease [6, 7].

Certain needs, such as special meals and in-flight oxygen, should be arranged with the carrier at least 48 hours prior to departure. Aisle or bulkhead seats allow greater leg room and comfort, and can be requested at the time of booking. Intestinal gas expands with altitude, and avoidance of food or carbonated beverages that cause bloating is advisable. Comfortable, non-constricting clothing should be worn during travel. Excessive alcohol and caffeine may lead to dehydration and worsen fatigue or jet lag.

All travellers should confirm their travel schedules prior to departure, and allow adequate time for travel to the terminal and for check-in. Arrangements with carriers for extra assistance or wheelchairs should be made in advance if possible, but help is often readily available within the terminal. Wheeled luggage requires less effort to transport and may be preferable for some travellers.

Medications and medical supplies

An adequate supply of all medications, enough for the entire trip plus at least several extra days' worth, plus other essential medical supplies (e.g. alcohol pads, syringes, needles) should be carried with the traveller or in hand luggage – not in checked baggage – to prevent theft or loss. Duplications of some medications may be critical. Commonly used non-prescription medications such as analgesics, antiemetics, antacids, decongestants, laxatives and hydrocortisone cream, as well as commonly used items including sunscreen and basic first aid supplies, may also be useful. Certain medications may ultimately require long-term refrigeration; the availability of suitable storage facilities at the destination should be confirmed. Medications that may be ineffective when expired, such as sublingual nitroglycerine, should be refilled prior to travel. Because the composition and potency of some medications may vary according to manufacturer, and not all medications are available in every country, loss of such medications can pose significant problems. Also, drugs in parts of the developing world are not uncommonly counterfeit or of poor quality, which is why it is paramount for the traveller to carry a full supply.

Prescription medications should be carried in their original labelled containers. A list of all medications (generic names) and special supplies, with indications for them, should also be carried with the traveller. Prescriptions, or a physician's letter on letterhead paper that can be presented to customs and law enforcement officials, provide legitimate documentation of needs for specific medications and supplies (e.g. narcotics, needles, syringes, oxygen) that might otherwise hinder travel across international borders. Some prescription medications may be prohibited in certain countries (e.g. amphetamines cannot be brought into Singapore). Administration times of medications should be altered gradually, over several days, when multiple time zones are crossed. Modification of insulin dosing is outlined in the section on diabetes.

Trip cancellations and medical insurance

Travellers should verify the extent of medical coverage that their health insurance provider offers for travel outside their home country and ensure that any supplemental medical insurance, if required, is purchased prior to departure. Travel insurance is available through health insurance providers as well as through major credit card companies. Insurance should be sufficient to cover the costs of emergency medical care, as well as evacuation and repatriation costs. There may be restrictions as to what conditions will be covered by supplemental insurance, and this should be clarified with the insurance carrier. For many out-of-country medical services the traveller will be required to pay at the time the service is provided, with subsequent reimbursement from the insurance company.

Medical services abroad

Travellers should carry the name and telephone number of their physician(s), as well as that of a family member or friend to contact in the event of an emergency. They must be advised to seek medical attention urgently if a febrile illness develops or persists after they have returned home. Selected resources for travellers with special needs are listed at the end of the chapter.

When ongoing medical care such as haemodialysis is required during travel, arrangements should be made in advance by having the traveller's physician contact an appropriate specialist at the destination. A list of English-speaking physicians throughout the world is available from the International Association for Medical Assistance to Travellers (www.iamat.org). Subscribers to Shoreland's EnCompass service, a web-based travel medicine resource, have access to information concerning healthcare facilities in a number of developing countries. Embassies and consulates abroad may also be able to provide travellers with a list of local English-speaking physicians.

Medical records

The traveller should carry a summary of any significant past medical problems, including known allergies. A recent electrocardiogram (ECG) for those with cardiac disease is advisable, especially recordings with and without pacing for travellers who have pacemakers. The make, model and lot number of implanted devices (e.g. pacemakers, defibrillators and prosthetic cardiac valves or joints) and date of insertion should be recorded. Copies of other significant and relevant laboratory results should also be carried.

Considerations for all high-risk travellers

Travellers' diarrhoea

Perhaps the most common problem about which a traveller should be well versed is an approach to travellers' diarrhoea. Many travellers, often older persons, are at increased risk of acquiring travellers' diarrhoea due to reduced gastric acidity from achlorhydria, gastrectomy, H_2 blockers or proton pump inhibitors. Others, such as those with congenital and acquired immunodeficiency states, are at increased risk of developing disseminated infection from travellers' diarrhoea. While travellers with other medical conditions are not necessarily at increased risk of acquiring travellers' diarrhoea, prevention of enteric infection by planning safe food and water choices is particularly important for those in whom complications such as dehydration and electrolyte imbalances are more poorly tolerated and may result in serious morbidity, especially those with diabetes or underlying cardiac, renal, gastrointestinal or immune disorders. Infection and dehydration in individuals with diabetes increases blood glucose levels and more commonly results in hospitalisation than in normal individuals [8, 9].

Preventive measures and supportive therapy should be reviewed, as well as the indications for empiric antimicrobial therapy. Instruction on the use of rehydration salts for severe diarrhoea-related fluid loss is of paramount importance. Antimotility agents such as loperamide and diphenoxylate can improve diarrhoea, although diphenoxylate is a narcotic that should be used with caution in the elderly, and anticholinergic effects may lead paradoxically to abdominal distension, constipation or paralytic ileus. The older traveller may be wise to begin antimicrobial therapy early in an illness in order to minimise the risk of complications. A fluoroquinolone is still the treatment of choice for travellers' diarrhoea in most regions of the world; the dose must be reduced if renal failure is present, and caution is advised with coadministration of theophylline preparations because the quinolones increase serum theophylline levels. Alternatives include azithromycin (preferred for travel to south and southeast Asia, where fluoroquinolone-resistant *Campylobacter* is prevalent) or the non-absorbable antibiotic rifaximin.

Prophylactic antimicrobial agents for travellers' diarrhoea are generally not recommended for the healthy traveller; exceptions include those who cannot afford to be ill during travel and those with a 'bad track record' for travellers' diarrhoea. However, prophylaxis should be considered for travellers who are at increased risk of acquiring travellers' diarrhoea, of suffering severe medical consequences should

it develop, or of developing disseminated infection. While ciprofloxacin has been commonly prescribed for this purpose, rifaximin is also effective for this indication [10]. Chemoprophylaxis should begin 1 day before departure and continue until 2 days after the last exposure, for a maximum of 3 weeks.

Venous thromboembolism and travel

Travellers have an increased risk of venous thromboembolic disease, including both deep venous thrombosis (DVT) and pulmonary embolism (PE); reported rates from several observational studies range from 0 to 12% of travellers [11]. A significant proportion of these events will develop after the first week following travel [12]. The heterogeneity of the many studies performed to date, including differences in study design, timing and duration of follow-up, outcome measurements and diagnostic testing methods, and selection of travellers (and control groups, for case-control studies), precludes comparisons of different studies. Regardless, several recent meta-analyses and systematic reviews [11, 13, 14] indicate that the risk of venous thromboembolism (VTE) is increased two- to fourfold in travellers compared with the general population, in whom the estimated incidence of VTE is two to three per 1,000 people per year (or 0.1% of the general population) [15]. However, the majority of outcomes reported have been asymptomatic DVTs, the clinical significance and natural history of which are unclear, and which presumably resolve spontaneously without ever becoming clinically evident [11]. Philbrick [11] estimated that 0.05% of travellers will develop a clinically significant DVT, and that the risk of a symptomatic PE is 27 per 1 million flights. Risk factors for travel-related VTE include increasing duration of flight, particularly beyond 6 hours, as well as known risk factors for VTE such as increasing age, a history of prior DVT or PE, thrombophilia, obesity, prolonged immobilisation, malignancy and venous stasis including varicose veins.

Many recommendations for preventing VTE during travel, including wearing loose clothing, contracting leg muscles frequently while seated, taking frequent short walks when safe to do so, and ensuring adequate hydration with non-alcoholic beverages, are sensible and feasible but have not been proven to reduce VTE risk. Immobility, dehydration, lower leg oedema, hypoxia and the hypobaric conditions within an aircraft cabin may contribute to a thrombophilic state (as determined by measurements of clotting factors), but their role in the development of travel-related VTE is unclear. Compression stockings have been shown to be beneficial for prevention of asymptomatic DVT in two meta-analyses to date [16, 17], both showing a 90% or greater risk reduction based on the studies included, but their effect on clinically apparent VTE is unknown. Aspirin and subcutaneous heparin are generally not recommended for prophylaxis in most travellers, but the latter may be indicated for selected (high-risk) patients.

The traveller with diabetes

It is clear that individuals with diabetes mellitus travelling abroad experience problems. One recent study reported that 10% of diabetics using insulin experienced problems while travelling, mostly due to hypoglycaemia [18]. In addition, most diabetic patients wanted more advice to be available at the travel clinic. In this section, we review how persons with diabetes should prepare for travel, adjust insulin preparations during travel, and manage diabetes and infectious complications. General advice including current United States Transportation Security Administration (TSA) guidelines for travellers with diabetes is outlined in Table 27.2.

Patient education may help to reduce the incidence of problems related to travel for those with insulin-dependent diabetes as well as those with type 2 diabetes. It is most important for individuals with diabetes to carry an adequate supply of everything required for diabetes care (and any other medical conditions) on their person during travel, including an additional 50% supply of medications as well as food, meals, glucose tablets and glucagon in case of unforeseen transportation delays. Travellers can check with their national diabetes association, e.g. the American Diabetes Association (ADA) website (www.diabetes.org); Diabetes UK website (www.diabetes.org.uk); Diabetes Australia website (www.diabetesaustralia.com.au), and with the airline carrier to confirm the airline's policy regarding carrying diabetes medication and supplies. Travel plans may be an excellent stimulus for joining the supportive ADA, which can provide educational material and other support for travellers with diabetes. The ADA provides services including patient monographs on pertinent subjects such as eating out, and a buyer's guide for diabetes supplies at home and abroad. It would be worthwhile for travellers with diabetes and their travelling companions to know how to tell someone, in the local language, that they have diabetes and how to request sugar or orange juice should they experience an episode of hypoglycaemia. Individuals with diabetes should obtain and carry a diabetes alert card, available in several languages from the ADA, and wear a medical bracelet as well. The ADA and other groups have valuable resources for travellers with diabetes, including the Diabetes Monitor (www.diabetesmonitor.com), which contains an edition entitled 'Travelling with Diabetes'. The International Diabetes Federation (www.idf.org) provides a list of regional and

Table 27.2 Tips for travellers with diabetes

Preparation before the trip
- Have a medical exam and make sure diabetes is in good control
- Receive standard immunisations and travel advice
- Obtain two sets of documents:
  - doctor's letter that lists medications, need for syringes and glucometers, allergies
  - prescriptions for drugs
- Get a medical ID bracelet that indicates that you have diabetes, and a diabetes alert card
- Learn to say 'I have diabetes' and 'sugar and juice please' in the local language of the country you are visiting
- When flying, request a special meal low in sugar, fat and cholesterol, at least 48 hours prior to departure

Packing tips
- Pack at least 50% more medication and blood testing supplies as predicted, and carry this with you
- Antibiotics, antidiarrhoeals, antinausea medications, and a packaged snack to treat low glucose should always be handy
- Gels or liquids required for treatment of hypoglycaemia are acceptable; however, if containers hold more than 3 oz (84 ml) these must be declared to security personnel

Travelling with insulin
- Insulin, insulin dispensing products and any other liquid medications (e.g. glucagon) should be labelled with the traveller's name (must match name on travel documents)
- Insulin pumps and supplies must be accompanied by insulin with a label clearly identifying the medication
- If using an insulin pump, advise the security screener that the pump cannot be removed. Pumps can safely go through airport security systems. If a visual inspection is requested, be prepared for increased scrutiny or a pat-down
- The following must be screened but are also permitted through TSA security checkpoints in the US:
  - unlimited number of used syringes, when accompanied by insulin or other injectible medication
  - blood glucose meters, blood glucose meter test strips, continuous blood glucose monitors, lancets, alcohol swabs, meter-testing solutions and monitor supplies
  - insulin pump and insulin pump supplies (cleaning agents, batteries, plastic tubing, infusion kit, catheter and needle)
  - urine ketone test strips
  - unlimited number of used syringes when transported in an appropriate sharps disposal container
- Use the same insulin regimen that you currently use, noting that travelling eastward shortens the day, so less insulin is required, and travelling westward prolongs the day so more insulin is required
- Insulin does not need to be refrigerated, but should be stored at moderate temperatures. Insulin at extreme heat or cold can degrade
- Insulin should not be exposed to direct sunlight
- Ensure that insulin concentrations are correct, that the syringes being used are appropriate for the insulin preparation, and that doses are carefully measured
- Check blood glucose frequently

country email addresses should one require specialist care abroad.

Although there is no evidence that individuals with type 1 diabetes are at increased risk of travellers' diarrhoea, they are at risk for complications should it develop. Furthermore, it has been reported that many with diabetes inappropriately refrain from treating their diarrhoea with oral rehydration solutions that contain carbohydrate, a widely used substrate to enhance sodium absorption [19]. However, one very small study on this topic demonstrated only non-significant increases in blood glucose levels in patients taking oral rehydration solutions that contained either glucose or rice, suggesting that such preparations can be safely used by patients with type 1 diabetes [20]. Education regarding the use and safety of oral rehydration solutions is essential.

Malaria prevention advice is no different for travellers with diabetes than it is for healthy individuals. It is also important to ask about any recent surgery. For example, for 1 year after laser treatments, the diabetic retina may not respond well to hypoxia from prolonged air flights requiring pressurised cabins. Remind the traveller to seek advice from their ophthalmologist regarding the risk of recent eye treatments.

Vaccine considerations for travellers with diabetes

Immunisation is essentially no different for travellers with diabetes; however, live influenza virus vaccine should be avoided, as subtle immune deficits exist which may lead to increased adverse effects. No documented increased risk of adverse effects exists for other live virus vaccines, such as MMR and yellow fever. Given the possibility of need for hospitalisation abroad, travel medicine consultants should encourage completion of the hepatitis B vaccine series by standard or accelerated schedule and provide a frank discussion of hepatitis B risk. Travel to regions and during seasons endemic for Japanese encephalitis warrants a strong recommendation for use of the newer safer formulation of this vaccine. The risk of developing encephalitis is higher in persons with diabetes who are exposed to Japanese encephalitis virus than among healthy individuals, due to their subtle immune deficits [21].

Immunisations should include annual influenza vaccine and pneumococcal vaccine. Tuberculin skin testing using purified protein derivative (PPD) should be performed before and after any travel that includes added tuberculosis risk, such as medical work in endemic regions or prolonged travel with close contact with the local population. The risk of tuberculosis for those with diabetes is also several-fold higher than that of the general population.

Common infections in the traveller with diabetes

Travellers with diabetes are at risk for other serious infections while travelling abroad due to the combination of factors such as neuropathies, vascular compromise and abnormal phagocytic cell function. Prevention strategies and early antibiotic treatment of routine problems can help avoid life-threatening infectious syndromes in persons with diabetes. Appropriate self-medication strategies for several issues should be set in place before travel.

Skin and soft tissue infections

Individuals with diabetes have a predilection for cutaneous infections caused by Gram-positive pathogens. Diligent foot care is of paramount importance. Unnoticed foot trauma from new footwear or hiking shoes may lead to diabetic foot ulcers and osteomyelitis. Careful instructions regarding avoidance of new shoes, frequent changes of socks to avoid persistent pressure points, examination of feet each night, and local care of early ulcers should be provided. Management of foot injuries with wound dressings and antibiotics for possible early infection are necessary to prevent cellulitis, lymphangitis and more severe local (e.g. pyomyositis) and systemic infection. Both staphylococci and group B streptococci are important pathogens under these circumstances. The increasing prevalence of methicillin-resistant *Staphylococcus aureus* strains has further complicated antibiotic treatment, and the use of trimethoprim-sulfamethoxazole can be offered for initial treatment of cellulitis for this reason.

Pyomyositis

The traveller with diabetes who engages in strenuous sports or long arduous treks adds additional risk factors for the development of serious skeletal muscle infection with *S. aureus*. Strenuous muscle activity, local abrasions, cutaneous infections during travel, insect bites and muscle trauma in particular [22] can predispose to muscle infection in individuals with diabetes. Pathogens are predominately *S. aureus*, but also include other species such as group B, C and G streptococci, and occasionally facultative Gram-negative organisms or anaerobes.

Urinary tract infections

These are more common in women with diabetes, particularly if fluid intake has been decreased. Risk during travel may be associated with increased sexual activity on vacation. Gram-negative enteric flora or enterococci are the major offenders, unless there has been prior use of antibiotics, or vaginal candidiasis is present. Upper tract disease (renal carbuncle, perinephric abscess or renal papillary necrosis) occurs more commonly in individuals with diabetes. This emergency should be anticipated and a 2-week antibiotic regimen (e.g. with a broad spectrum antibiotic such as a newer fluoroquinolone, which can also be used to treat many skin, respiratory and gastrointestinal infections) offered to treat such infections, with hopes of averting hospitalisation.

Community-acquired pneumonia

This may be more severe in individuals with diabetes and it may require both hospitalisation and broader antibiotic coverage for other organisms which are less common in those without diabetes, such as *S. aureus*, Gram-negative organisms or even *Mycobacterium tuberculosis*. Oral antibiotics may not always prove to be adequate for all infections in persons with diabetes. Nephrotoxic agents must be avoided, particularly when renal insufficiency is already present, as should the additional burden of ototoxic drugs in patients who already have the potential for impaired vision from diabetes.

Candidasis

Persons with diabetes are readily colonised and develop clinical infections with *Candida* spp. Patients receiving oral doxycycline for malaria prophylaxis would be at particularly increased risk, and should be prepared to self-treat the first appearances of candidal infections.

Melioidosis, insulin and diabetes

The medical literature originating from geographic areas where melioidosis is an endemic disease, such as Southeast Asia and northern Australia, refers frequently to its clinical associations with diabetes mellitus. The causative organism, *Burkholderia* (formerly *Pseudomonas*) *pseudomallei,* has a unique ability to bind human insulin, and this bacterial property may underlie a remarkable biological and clinical relationship, with important implications for travellers with diabetes to endemic areas [23]. The disease gained notoriety during both the French and American involvement in Indochina, such that by 1973 more than 340 cases had been described among American soldiers fighting in Vietnam, with helicopter pilots at greater risk of infection from soil blown around by rotor blades. The geographic extent of disease distribution was later found to reach the northern rice-growing regions of Thailand, Australia and even the Caribbean basin, and continues to expand.

Burkholderia pseudomallei can be isolated from both soil and water, and is particularly prevalent in rice paddies during the rainy season. Infections seem to be acquired by several routes, including inoculation and inhalation. Melioidosis is a seasonal disease, with the majority of cases occurring during the rainy seasons among those who are regularly in contact with soil and water. Males predominate and the incidence is highest in those between 40 and 60 years of age.

In endemic regions, melioidosis accounts for an unusually high proportion of community-acquired sepsis, being the most common source of fatal community-acquired sepsis in the northern territories of Australia. Most patients have an underlying metabolic or disease process, such as alcohol abuse, an immunosuppressive disorder, diabetes mellitus, renal disease, liver disease or pregnancy, although melioidosis does not appear to be an AIDS-associated opportunistic infection. Melioidosis may be localised or disseminated and might only present clinically after many years of bacterial latency.

Travel medicine consultants should be aware that those with diabetes (both type 1 and type 2) who have the appropriate exposure to infected soil and water are clearly predisposed to severe melioidosis when physiologic insulin levels are not maintained. Although type 1 diabetes and insulin deficiency do not fully explain the predisposition for melioidosis, human insulin levels appear to appear to play a unique role in modulating the pathogenesis of infection and septicaemia associated with melioidosis. Emerging epidemiological data should be reviewed and appropriate advice regarding the risks of acquiring melioidosis should be provided to travellers, particularly those with diabetes.

Management of diabetes

Individualised advice by expert personnel regarding insulin management during travel is ideal, provided a simplified approach is offered. It is best for travellers with diabetes to have a thorough understanding of their disease and full medical evaluation before their departure. Travel results in extraordinary exertion, interruptions in routines and meals, and sometimes nausea, vomiting and diarrhoea, which require special management in travellers with diabetes. Tight glucose control carries the risk of hypoglycaemic episodes in the face of acute illness and while crossing multiple time zones. A safer approach is to advise the traveller to accept higher than normal glucose readings during travel. More frequent blood glucose monitoring is the best way to avoid the serious consequences of hypoglyacemia and to determine insulin needs. Keeping track of elapsed time during travel is the most challenging part. Travellers requiring insulin should be instructed to check their blood glucose every 4–6 hours while en route and crossing multiple time zones, even if they are not accustomed to such frequent monitoring. Travellers on oral hypoglycaemics do not require additional doses and should take their medication according to local time; however, care should be taken to avoid missing meals. Omitting the evening dose on eastbound flights results only in tolerable elevated blood glucose levels and will help avoid hypoglycaemia, rather than taking doses too close together. For insulin users, north–south travel and crossing fewer than six time zones also requires no adjustment of insulin dosing schedules. Crossing six time zones or more while travelling eastward leads to a shortened day, and less insulin will be required. Sane *et al.* [24] suggest decreasing the daily dose of insulin by 2–4% for each hour of time shift during eastward flights, and increasing dosing by the same amount for westward flights. Good examples of individualised insulin regimens are available at www.diabetesmonitor.com. Cultural and religious issues may include fasting as an important part of the traveller's plans and such risks should be drawn out and addressed during the consultation.

Insulin preparations vary, and advances in diabetes care with availability of pre-filled syringes and cartridges can ease administration and storage during travel. There are numerous types of insulin manufactured in the US alone, which may cause confusion and error while abroad. In addition,

insulin preparations in the US are now all U-100 strength but they can still be sold as U-40 or U-80 abroad. Use of a U-100 syringe with these preparations would result in underdosing with insulin. Travellers with diabetes may benefit from using newer insulin analogs due to their convenience and short-acting property, although they tend to be more expensive than regular insulin [25]. Three rapid-acting insulin analogs are currently available: insulin lispro, insulin aspart and insulin glulisine. All three are approved for use in both type 1 and type 2 diabetes by subcutaneous injection, insulin pump or intravenous administration [25]. These products are produced via recombinant DNA technology and have less tendency than regular insulin to form hexamers that slow absorption. This offers a more rapid onset and shorter duration of action and allows individuals to time their injection immediately before a meal instead of a planned 30 to 40 minutes prior, in turn leading to a better match between carbohydrate absorption and insulin availability with less chance for late-peaking regular insulin to cause dangerous postprandial hypoglycaemia. Details on these insulin preparations can be found in additional excellent resources [www.diabetesmonitor.com; [26, 27]]. There are also new injectable agents available for type 2 diabetes treatment that travellers with diabetes may use [28].

Altitude and diabetes

Travel to high altitude, defined as 3,000–5,000 m (10,000–16,000 ft), and extreme altitude over 5,000 m pose added risk and complexity to the traveller with diabetes. Exercise is an important adjunct to diabetes care and is highly recommended by the ADA and other similar national associations. Increasing numbers of people with type 1 diabetes now participate in extreme forms of physical activity, including high-altitude trekking and mountain climbing. An excellent review provides terrific detail and a summary of research on the challenges of exercise at high and extreme altitude in individuals with diabetes [8]. To highlight some issues for travellers with diabetes, several symptoms of acute mountain syndrome such as headache, nausea and dizziness make it difficult to recognise hypoglycaemia. Altitude-induced anorexia may lead to postprandial hypoglycaemia. While there are no reported cases of high-altitude cerebral oedema or high-altitude pulmonary oedema in persons with diabetes, these can be fatal if not identified and treated. There are two case reports of ketonuria and two other cases of ketoacidosis among 15 individuals with type 1 diabetes who climbed Mount Kilimanjaro [29]. High-altitude retinal haemorrhage is a relevant issue to consider for the individual patient. A dilated pupil ophthalmologic examination and/or fluorescein angiogram are recommended before considering trips involving exposure to high altitude.

Glycaemic control decreases in normal individuals at altitude. These individuals respond with elevated catecholamines, which in turn increase insulin secretion. Persons with type 1 diabetes may be particularly susceptible to stress-induced hyperglycaemia unless insulin doses are adjusted appropriately. Ascent to extreme altitude is associated with further insulin resistance. Optimal management of glycaemia requires frequent blood glucose monitoring combined with the ability to acutely change insulin dosing regimens. Sporadic hypoglycaemia has also been reported, likely related to an inappropriate balance between insulin dose, high-intensity exercise and food intake. To complicate this management further, glucometers are unreliable at altitude. [29, 30] Documented significant falsely high and falsely low readings – by as much as 37% – may occur due to low temperatures affecting the equipment and the batteries [8].

To facilitate desired physical activity in this group, additional education is indicated and caution is warranted. Altitude treks are contraindicated for persons with known coronary disease, as increase in altitude is accompanied by increase in heart rate and blood pressure. We suggest screening individuals with diabetes for silent ischaemia to identify those who truly may deteriorate at high altitude. Brubaker [8] advises that individuals carry multiple meters and hold equipment next to the skin, which may prevent the problems with meter and battery malfunction at low temperatures. Insulin should not be exposed to temperatures below 2°C or it may freeze or simply become inactive, and additional supplies of insulin should be available in the event of an emergency.

Considerations for travellers with other chronic medical conditions

Cardiovascular disease

Cardiovascular diseases, including myocardial infarction and cerebrovascular events, are the leading causes of death, accounting for approximately half (or more) of all deaths in travellers; most occur in those aged 55 years older [1–3, 31]. Of 782 deaths due to natural causes in overseas visitors to Australia between 2001 and 2003, ischaemic heart disease accounted for 40% of male and 25% of female deaths [3]. Cardiac events accounted for 11% of medical emergencies in travellers at the Seattle-Tacoma International Airport over a 1-year period, occurring both within the airport, where they accounted for 7% of all airport emergencies, and in the air, where they accounted for 20% of all in-flight emergencies [32]. Cummins *et al.* [33] reviewed 577 deaths that occurred during flight between 1977 and 1984, of which 56% were attributed to cardiac events. Most (66%) occurred in

men, with a mean age of about 54 years. Strikingly, cardiac deaths in apparently healthy travellers were common, accounting for 63% of all deaths in this group and 78% of all sudden cardiac deaths. Sudden cardiac events during flight frequently necessitate unscheduled landings, which can be especially problematic during overseas flights.

Cardiac contraindications to flying are listed in Table 27.1. Implanted cardiac devices are not contraindications to flying. Proper functioning of such devices should be ensured prior to travel, and batteries replaced if needed. Electronic pacemaker checks by phone cannot yet be relayed by satellite from overseas destinations, but relay will soon be available aboard aircraft. It may be prudent to determine the facility closest to the travel destination that is best equipped to service travellers with such devices in the event of an emergency. It is important to note that portable security magnets may interfere with the functioning of an implantable defibrillator; a physician's letter may be useful for such travellers. Travellers with cardiac conditions should carry a recent ECG in case they require medical care while abroad. Guidelines for assessing oxygen requirements are discussed in the following section.

Pulmonary disease

Most commercial aircraft cruise at altitudes between 22,000 and 44,000 feet (6,706–13,411 m) above sea level. Cabin pressure equivalent to sea-level pressure can be maintained up to an altitude of roughly 22,500 feet (6,858 m). Above this altitude, the partial pressure of oxygen begins to fall and active cabin pressurisation is required, resulting in an atmosphere equivalent to that found between 5,000 and 8,000 feet (1,529 and 2,438 m) above sea level. Active cabin pressurisation can adversely affect sinusitis and otitis.

Air travel is contraindicated in those with pneumothorax or pneumomediastinum, and should be delayed for several weeks following middle ear or thoracic surgery (Table 27.1). The reduction in atmospheric oxygen during flight, while well tolerated by healthy travellers, can lead to marked hypoxaemia in travellers with cardiopulmonary compromise, although the clinical significance of this is not completely clear [34–37]. Dillard *et al.* [38] found that pulmonary symptoms, including dyspnoea, oedema, wheezing, chest pain and cyanosis, worsened during flight in 8 of 44 travellers (18.2%) with chronic obstructive lung disease. Akero *et al.* [36] performed in-flight assessments during an international flight of 5 hours 40 minutes duration on 18 individuals with chronic obstructive pulmonary disease deemed to be fit to fly (resting pO_2 94% at sea level and self-reported ability to walk 50 metres without severe dyspnoea). The majority tolerated hypocarbic hypoxia well at rest. With light exercise, two individuals reported moderate to strong dyspnoea, increasing to seven (39%) when walking, and one of these individuals had associated headache.

The minimum desired PaO_2 during flight is 50 mmHg, and supplemental oxygen should be used if the predicted PaO_2 will be below this level. The inspired oxygen concentration (FiO_2) required during flight can be estimated using several methods. Using a hypoxia-altitude simulation test (HAST), Gong *et al.* [39] determined that the arterial oxygen tension (PaO_2) measured at sea level in normocapnic individuals with chronic airway obstruction is the best predictor of the resting PaO_2 at a given altitude. They developed a nomogram that can be used to predict the estimated PaO_2 during flight. Using the HAST, a sea level PaO_2 of 72 mmHg correlates to a PaO_2 of at least 50 mmHg in a cabin altitude of 8,000 feet (2,438 m) in most normocapnic individuals.

The HAST nomogram can be used with the baseline PaO_2 measured using supplemental oxygen. Kelly *et al.* [40] have recently confirmed that the HAST is a good predictor of in-flight oxygen needs. A recent comprehensive review [41] provides guidance on of the use and interpretation of the HAST, as well as oxygen supplementation. An alternative to the HAST is a formula that also incorporates the measured forced expiratory volume in the first second (FEV_1) [42]:

$$PaO_2(\text{at } 8{,}000 \text{ feet}) = [0.519(PaO_2 \text{ at sea level})] + [11.855(FEV_1 \text{ in litres})] - 1.760.$$

For travellers who do not require supplemental oxygen on land, an FiO_2 of 30% (2 l/min) should be adequate. Regardless of the method used, the PaO_2 (and FEV_1, if used) should be measured within 2 weeks of scheduled travel.

Pulmonary function should be optimised prior to and during flight by using bronchodilators and/or corticosteroids, if indicated. A prescription for supplemental oxygen (indicating the flow rate or FiO_2, and specifying continuous versus intermittent oxygen) is required, as is a physician's letter outlining the individual's fitness to travel. In-flight oxygen and equipment will be supplied by the carrier, at a cost to the traveller, usually based on flight segments and/or the number of oxygen canisters required. Check with the air carrier for charges, and be aware that delivery systems may vary. Airline attendants can provide basic assistance such as changing canisters, but should not be expected to assist if mechanical problems arise. If oxygen is required during lay-overs or at the final destination(s), delivery should be arranged well in advance. The traveller's regular oxygen vendor should be able to assist with these arrangements. Payment may be required when services are delivered, and may or may not be reimbursed by insurance plans.

Adequate hydration will facilitate the clearance of pulmonary secretions in bronchitic travellers. Tracheostomies should not be expected to pose significant problems during

travel, and the traveller should bring any equipment required for care.

Gastrointestinal disorders

Travellers with reduced gastric acidity or inflammatory bowel disease may benefit from antibiotic prophylaxis. Because intestinal gas expands with altitude, air travel following abdominal surgery should be delayed for several weeks if possible. Travellers with colostomies should use a larger bag and have an extra bag on hand for the same reason.

Mefloquine is metabolised in the liver and should be avoided in persons with significant liver impairment. Travellers' diarrhoea may lead to serious dehydration and loss of intravascular volume, and empiric antibiotics are warranted. In addition, travellers with cirrhosis are at increased risk of acquiring severe gastrointestinal or cutaneous *Vibrio vulnificus* infections from seafood or salt water exposure, particularly along the Atlantic and Gulf coasts in the US.

Renal disease

Travellers with chronic renal disorders should also be offered antimicrobial chemoprophylaxis for travellers' diarrhoea, with appropriate dose adjustments if required. Dehydration may worsen chronic renal failure and precipitate nephrolithiasis; adequate hydration in warm climates is advised. Adherence to dietary restrictions for those with chronic renal disease may be difficult, and travellers should be advised to investigate local food choices prior to travel.

Proguanil, an older antimalarial that is being used more often for prophylaxis and treatment of malaria as part of the combination drug atovaquone-proguanil (Malarone), is excreted renally. Renal impairment may lead to its accumulation, which in turn may lead to folate deficiency. Individuals with renal impairment should take folic acid supplements when using proguanil [43]. Atovaquone-proguanil (Malarone) is contraindicated in those with severe renal insufficiency (creatinine clearance <30 ml/min).

Travellers on dialysis

Dialysis should not preclude travel, but advanced planning is essential. Peritoneal dialysis can be managed with relative ease during travel, provided the necessary equipment and dialysis solutions can be transported and/or delivered reliably. Haemodialysis is available worldwide, but several months' notice may be required for scheduling. Some units will require hepatitis B, hepatitis C and HIV testing to be performed, and may refuse to dialyse individuals with any of these infections. Careful scrutiny of which dialysis centre to choose is important, as blood-borne pathogens may be easily transmissible in a dialysis unit if there is a break in technique or repeat exposure to blood products. Epidemic transmission of HIV in renal dialysis centres in Egypt was reported 7 years after the documented event [44]. Hepatitis C has also been a concern among travellers requiring haemodialysis abroad [45–47]. Hepatitis B vaccination using a high-dose vaccine should be ensured in non-immune haemodialysis patients prior to travel. The traveller's dialysis unit and local branches of the Kidney Foundation should be able to provide information and help with arrangements. A list of dialysis centres throughout the world can be obtained from Global Dialysis (www.globaldialysis.com). Some travel and cruise companies also offer trips specifically tailored for dialysis patients.

Anaemia

Hypoxaemia with altitude may adversely affect travellers with severe anaemia (haemoglobin <7.5 g/dl or 75 g/l) and sickle cell disease. If anaemia is not correctable with red blood cell transfusion, supplemental oxygen should be used during flight.

Orthopedic conditions

Travellers with lower extremity fractures should keep the leg elevated as much as possible, to reduce swelling and circulatory impairment. A bivalved cast that can accommodate some limb expansion may also be helpful. Some orthopaedic fixation devices can trigger security alarms at airports; a physician's letter outlining the presence of the device can be useful in case this occurs. Subcutaneous heparin to prevent DVTs should be considered in these individuals on long flights.

Neuropsychiatric disorders

Persons with active depression or history of psychiatric disorders should not use mefloquine. In addition, mefloquine may lower the threshold for seizure activity and persons with a history of a seizure disorder must avoid use of mefloquine. Persons with acute psychiatric disorders must avoid travel unless they are accompanied by an escort who will carry and administer appropriate medication. Others with stable conditions should remain on their medications and ideally travel with a companion.

Seizure disorders

Air travel is not contraindicated in individuals with seizure disorders, but seizures should be well controlled.

Modification of therapy prior to travel is probably unnecessary, contrary to many airlines' recommendations [48]. Travellers with epilepsy should inform flight attendants of their disorder.

Scuba diving is risky for healthy individuals as well as those with epilepsy. Apart from the risk of drowning, the main physiological problems caused by exposure to gases at depth are decompression illness, oxygen toxicity and nitrogen narcosis. A seizure occurring underwater while using conventional scuba equipment is usually a fatal event. The mouthpiece is likely to be lost with subsequent inhalation of large quantities of water during the clonic phase of the seizure. The British Sub-Aqua Club as well as the United Kingdom Sport Diving Medical Committee state that 'it is imperative that no epileptic should dive if there is any serious possibility of an attack occurring underwater' [www.diversalertnetwork.org; [49]]. The United Kingdom Sport Diving Medical Committee advises that in order to dive, someone with epilepsy must be seizure-free and off medication for at least 5 years. The reasons for this are largely theoretical. Almeida *et al.* [49] reviewed thoroughly the available evidence in the medical literature and diving websites. The risk of seizures recurring decreases with increasing time in remission, but the risk is never completely abolished. Individuals with epilepsy who wish to engage in diving, and the physicians who certify fitness to dive, should review all the available evidence and carefully consider the health of each traveller on an individual basis. The following criteria characterise divers who may be able to consider diving to shallow depths:

- those who are entirely seizure-free on stable antiepileptic drug therapy for at least 4 years
- those on non-sedating antiepileptic agents
- individuals who are sophisticated about their illness to understand the risks
- those who have a diving buddy who can accompany them and who also understand the risks.

Altitude issues

Ascent to high altitudes may trigger a migraine headache associated with new focal neurologic deficits [50]. Military studies report increased incidence of ischaemic stroke at high altitude predisposed by dehydration, polycythaemia and periods of forced inactivity [51, 52]. Persons with known structural abnormalities such as arteriovenous malformations or aneurysms may be at risk for rupture at high altitude and may be advised to avoid ascent above 3,000 metres. High altitude may lower seizure threshold. Anticonvulsant medication should be considered for persons with a history of seizures who are not currently on treatment and are travelling to high altitude, especially for extended trips above 2,500 metres. Persons with acute stroke including subarachnoid haemorrhage within 3 days, generalised seizures within 24 hours and brain surgery within 10 days must decline travel to altitude [53]. Guidelines published by the Aerospace Medical Association on Fitness for Travel are helpful [54].

Increased intracranial pressure and the post-neurosurgical state

Individuals with increased intracranial pressure should be advised against air travel. Rarely, undiagnosed cerebral mass lesions have presented during flight [55]. Postoperative pneumocephalus and the risk of tension pneumocephalus during transport can be life threatening. Evidence is contradictory yet some data suggest that postoperative 100% oxygen may improve the rate of pneumocephalus absorption. Of 17 airlines questioned in one survey, three offered substantive medical information while the rest deferred to the decision of the operating surgeon [56].

In aviation medicine, there are rare case reports and theoretical models of individuals who must travel by air after craniotomy. These discuss concerns of expansion of intracranial air with increasing altitude. A series of 21 patients with post-traumatic and/or post-craniotomy pneumocephalus was studied before and after long-range air evacuation [52]. Air volumes were calculated using a simplified method to err on the side of overestimation of pneumocephalus volumes, based on computerised tomography scans performed within 24 hours prior to air travel. Volumes ranged from 0.6 to 42.7 ml, with mean volume of 9.3 ml (median volume 4.3 ml). Persons with pneumocephalus had no permanent or even temporary decline as a result of air transport. The three patients who had continuous monitoring of intracranial pressures did not have sustained increased intracranial pressure during flight. Hence, aeromedical evacuation of patients with head injury may not be as dangerous as previously thought.

Special considerations for older travellers

Motion sickness

Non-pharmacological methods to reduce motion sickness include closing the eyes, focusing on the horizon, and limiting head and neck movements. Medications such as dimenhydrinate, diphenydramine and hyoscine can provide symptomatic relief but cause anticholinergic and other side effects, such as drowsiness and confusion, with increased frequency in elderly travellers. Hyoscine inhibits sweating and can contribute to heatstroke, particularly in warm

climates; it is contraindicated in individuals with glaucoma and prostatic hypertrophy.

Jet lag

Jet lag (circadian dyschronism) is more pronounced in the elderly, and with travel over more than five time zones and in an eastward direction. In general, travellers should be warned that each 1-hour time zone that is crossed will require 24 to 36 hours to acclimatise [57]. Dividing travel across many time zones into shorter segments may help the elderly traveller acclimatise better, albeit with more inconvenience to the traveller. A well-rested state and adaptation of normal routines to the current time of day on arrival at the destination can aid in reducing jet lag.

Caffeine consumption to stimulate daytime wakefulness may also further disrupt the sleep cycle by causing insomnia. Benzodiazepines, while providing some relief from sleep disturbances, may cause drowsiness, impaired memory and fatigue with increased frequency in the older traveller, especially in those unaccustomed to taking these medications. Zolpidem is a short-acting hypnotic agent that has been shown to be effective in improving sleep quality in travellers [58]. Melatonin, a naturally produced hormone which is currently available in the US as an unregulated nutritional supplement, is effective for ameliorating the effects of jet lag by improving sleep quality and decreasing daytime fatigue. The authors of one meta-analysis [59] concluded that doses between 0.5 and 5 mg daily taken close to bedtime at the destination were comparably effective in reducing jet lag, although self-reported sleep quality may be better with a 5 mg dose [60]. Melatonin for the treatment of jet lag is currently recommended by the American Academy of Sleep Medicine [61].

Heatstroke and hypothermia

The elderly are also more susceptible to the effects of extreme temperatures. Adapting to a different climate may take several days, during which limitation of outdoor activity is advisable. Gradual acclimatisation before travel, if possible, facilitates this adjustment. Adequate hydration and appropriate clothing are essential in both hot and cold climates. In hot climates, anticholinergic agents as well as beta blockers, calcium antagonists, diuretics, antihistamines and tricyclic antidepressants may impair thermoregulation, worsen dehydration or precipitate heatstroke.

Altitude and the elderly

Symptoms of altitude sickness, and its prevention and treatment, should be reviewed with all travellers who intend to ascend to altitude during travel. While a reasonable level of fitness should be ensured for elderly travellers who wish to participate in physical activities at high altitude, this will not provide any guarantee against developing altitude sickness. The effect of age on the risk of altitude sickness is unclear; some studies have suggested that the risk of altitude sickness is independent of age, whereas others suggest that increasing age confers a protective effect [62, 63]. Hypoxaemia and cardiac ischaemia may be precipitated by ascent to altitude, especially in those with underlying cardiopulmonary disorders (see section on Altitude and diabetes). With proper advice, including the need to ascend gradually and ensure sufficient time for acclimatisation, many elderly travellers can tolerate moderate altitudes (2,500 m) well. Preventive therapies including acetazolamide and steroids can be considered but may have an unfavourable side effect profile in the elderly.

Malaria

The incidence of severe illness and death due to malaria increases with age [5]. Personal protective measures apply to the elderly as they would to younger travellers. Potential neurotoxicity from DEET (N,N-diethyl-3-methylbenzamide) is not of concern for the elderly [64, 65]. Chemoprophylactic agents can be safely administered in the healthy older traveller and may in fact be better tolerated than in younger travellers [5]. Contraindications to mefloquine have been previously discussed. Chloroquine has rarely been reported to cause irreversible retinal damage when used in the presence of known retinal disorders, and severe, irreversible hearing loss has also occurred with brief exposure in individuals with pre-existing auditory disturbances. Alternatives should be considered in these instances.

Vaccine-preventable illnesses

Routine immunisations (MMR, polio, tetanus toxoid and varicella, as appropriate) should be updated prior to travel. One dose of 23-valent pneumococcal vaccine and annual influenza immunization are recommended for healthy adults 50 to 65 years and older, and for high-risk adults of any age.

Age alone is not a contraindication to any vaccine, although seroconversion rates may decrease with age. For the healthy older traveller, general recommendations for both routine and travel vaccines apply. The morbidity and mortality of hepatitis A increases substantially in the elderly, with a risk of death of 2–3% in those over 50 years of age. Hepatitis A seropositivity rates are also higher in older travellers who have lived in or travelled extensively to endemic areas, or have a prior history of jaundice; hepatitis A antibody screening prior to immunisation in these individuals may be

cost-effective [66, 67]. Immunologically impaired individuals, including those on haemodialysis, require a higher vaccine dose for hepatitis B (usually double, but consult the manufacturer's recommendations).

Elderly travellers are at higher risk of severe disease from yellow fever, but are also at increased risk of adverse events related to yellow fever vaccine. Based on passive adverse event reporting between 2000 and 2006, severe adverse reactions (including death, hospitalisation or prolongation of a current hospitalization, life-threatening illness, permanent disability or other medically important condition) occur in 4.7 per 100,000 people vaccinated overall, but the incidence increases to 12.6 per 100,000 in those over 70 years of age [68]. Viscerotropic and neurotropic reactions occur in 0.4 and 0.8 per 100,000 vaccine recipients overall, respectively, but increase to 1 and 1.6 per 100,000 in persons aged 60 to 69 years, and 2.3 per 100,000 (for both) in those 70 and older [68]. While many countries will require yellow fever immunisation for entry, based on the risk of vaccine adverse events it would seem reasonable not to immunise those older travellers who truly have an almost negligible risk of contracting yellow fever (e.g. travellers aboard cruise ships that stop at ports in South America). A medical certificate stating that vaccine is 'medically contraindicated' – a yellow fever exemption certificate – can be issued in these circumstances. It should be mentioned that in advance of travel to a country where a traveller may be exposed to a risk of yellow fever, the completion of a yellow fever exemption certificate should be reviewed and then renewed for each new trip.

Advice for the disabled traveller

The visually impaired traveller

Travellers needing spectacles should take an extra pair during travel, as well as a copy of their current prescription. Tools for emergency spectacle repairs, sold in pharmacies or at opticians' offices, may come in handy.

Contact lens wearers should take all required equipment and solutions with them, as well as an extra pair of spectacles. Iodine-purified water should not be used for lens care as it will permanently stain lenses. Daily disposable contact lenses are an attractive, relatively inexpensive, maintenance-free alternative to conventional contact lenses.

Blind travellers may prefer to travel with a companion, who may be eligible for discounted fares. If this is not possible, special arrangements can be made ahead of time to facilitate check-in, transfers, etc. Inquiries should be made at the time of booking. International travel with guide dogs can be a problem; certain countries will impose quarantine for imported animals. Travellers should contact the embassy or consulate of their destination(s) if considering travel with a guide dog, and should remember to inquire at home about restrictions for re-entry after travel.

The hearing-impaired traveller

Travellers who rely on hearing aids should carry extra batteries for their units. Hearing impaired and deaf travellers may also benefit from travelling with a companion, and discount airfares may apply. They should inform transportation carriers of their hearing impairment if overhead announcements are likely to go unheard, and can request that information be delivered to them individually. Some hotels will provide visual aids for the hearing impaired so that they can be alerted to alarms or phone calls. If these are unavailable, knowledge that a traveller is hearing impaired is essential, particularly in the event of an emergency. Teletypewriter (TTY) telephones may also be available and should be requested when making reservations.

The physically disabled traveller

The physically disabled traveller should discuss their specific needs with the travel agent. Facilities and assistance that can be provided during travel and at the destination(s) should be confirmed prior to booking. Help with boarding and disembarking may be requested and or required. Disabled travellers should not expect flight attendants to help them with eating, administering medications or providing assistance in washrooms. If the degree of assistance required during travel is beyond that which can be provided by flight attendants, the carrier may not allow travel unless the individual is accompanied. Discount fares for travel companions are often available. A recent ruling states that cruise ships, whether registered in the US or abroad, must accommodate disabled travellers under the Americans with Disabilities Act.

Personal mobility devices, including wheelchairs, canes, crutches and folding walkers, can usually be stored in the aircraft cabin. Transfer to smaller wheelchairs, which should be provided by the airline, may be required to board certain aircraft. Wheelchairs cannot yet be accommodated in most aircraft washrooms; the carrier can provide details regarding washroom space, if requested.

Wheelchair batteries may be damaged in baggage compartments. It is the airline's responsibility to transport mobility devices intact. If any device is damaged in transit, the carrier is obliged to pay for repairs or replace it with a similar model, and to provide a temporary replacement if needed. To avoid these problems, lightweight or smaller-sized, non-motorized wheelchairs may be preferable for travel. Tools for emergency repairs may be invaluable.

Summary

In summary, with appropriate and early preparation and a few extra precautions as well as self-treatment and prophylactic medications, high-risk travellers can enjoy exotic destinations and global travel in good health.

Selected additional resources

General information

Centers for Disease Control and Prevention Health Information for International Travel 2010: The Yellow Book; wwwnc.cdc.gov/travel/content/yellowbook/home-2010.aspx
Centers for Disease Control and Prevention Travelers Health; wwwnc.cdc.gov/travel/
The Australian Government's travel advisory and consular information service: Smartraveller www.smartraveller.gov.au/
The British Foreign and Commonwealth Office; www.fco.gov.uk/en/
United Kingdom Department of Health: Immunisation against infectious disease – 'The Green Book'; www.dh.gov.uk/en/Publichealth/Immunisation/Greenbook/DH_4097254
United States Transportation Security Administration; www.tsa.gov/travelers/index.shtm
World Health Organization International Travel and Health; www.who.int/ith/en/

Medical services

International Association for Medical Assistance to Travellers (IAMAT); www.iamat.org
International SOS; www.internationalsos.com
Medic Alert Foundation; www.medicalert.org
Shoreland's EnCompass; www.shoreland.com

Travellers with special needs

Travellers with diabetes

American Diabetes Association; www.diabetes.org; for information on travelling with diabetes, www.diabetes.org/living-with-diabetes/treatment-and-care/medication/when-you-travel.html
Diabetes Australia; www.diabetesaustralia.com.au
Diabetes Monitor; www.diabetesmonitor.com; for information on planning travel; www.diabetesmonitor.com/diet-and-lifestyle/plan-before-you-travel.htm
Diabetes UK; www.diabetes.org.uk
International Diabetes Federation; www.idf.org

Travellers on haemodialysis

Global Dialysis provides a list of worldwide dialysis centres; www.globaldialysis.com/
Kidney Health Australia; www.kidney.org.au/
National Kidney Foundation (United States); www.kidney.org; for advice on travelling with kidney disease; www.kidney.org/atoz/content/traveltip.cfm
United Kingdom National Kidney Federation; www.kidney.org.uk/

Travellers with other chronic medical conditions

United States Transportation Security Administration; www.tsa.gov/travelers/airtravel/specialneeds/index.shtm

Visually impaired travellers

American Council of the Blind; www.acb.org
Canadian National Institute for the Blind; www.cnib.ca
National Federation of the Blind; www.nfb.org
Royal National Institute for the Blind; www.rnib.org.uk

Hearing impaired travellers

Alexander Graham Bell Association for the Deaf; www.agbell.org
Canadian Association of the Deaf; www.cad.ca
National Association for the Deaf; www.nad.org
Royal National Institute for Deaf People; www.rnid.org.uk
World Federation of the Deaf; www.wfdeaf.org

Physically disabled travellers

Canadian Transportation Agency; www.cta-otc.gc.ca
Department for Transport (UK); www.dft.gov.uk/transportforyou/access
Mobility International USA; www.miusa.org
Society for Advancement of Travel for the Handicapped; www.sath.org
United States Department of Transportation Federal Aviation Administration; www.faa.gov/passengers/prepare_fly/#disabilities

References

1. Hargarten SW *et al.* (1991) Overseas fatalities of United States citizen travellers: an analysis of deaths related to international travel. *Ann Emerg Med* **20**: 622–626.
2. MacPherson DW *et al.* (2007) Death and international travel – the Canadian experience: 1996–2004. *J Travel Med* **14**: 77–84.
3. Leggat PA and Wilks J (2009) Overseas visitor deaths in Australia, 2001–2003. *J Travel Med* **16**: 243–247.
4. Guptill KS *et al.* (1991) American travel deaths in Mexico. Causes and prevention strategies. *West J Med* **154**: 169–171.
5. Dessery BL and Robin MR (1997) The aged, infirm, or handicapped traveller. In: DuPont HL and Steffen R (eds) *Textbook of Travel Medicine and Health*, pp. 455–464. BC Decker Inc., Hamilton, Ontario.
6. Hultgren NH (1990) Coronary heart disease and trekking. *J Wilderness Med* **1**: 154–161.

7. Backer H (1997) Medical limitations to wilderness travel. *Emerg Med Clin North Am* **15**: 17–41.
8. Brubaker PL (2005) Adventure travel and type I diabetes. *Diabetes Care* **28**: 2563–2572.
9. American Diabetes Association (2005) Standards of medical care in diabetes (Position Statement). *Diabetes Care* **28**: S4–S36.
10. DuPont HL *et al.* (2005) A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travellers' diarrhea. *Ann Intern Med* **142**: 805–812. Erratum, Ann Intern Med 1423, 239.
11. Philbrick JT *et al.* (2007) Air travel and venous thromboembolism: a systematic review. *J Gen Intern Med* **22**: 107–114.
12. Peerz-Rodriguez E *et al.* (2003) Incidence of air travel-related pulmonary embolism at the Madrid-Barajas airport. *Arch Intern Med* **163**: 2766–2770.
13. Kuipers S *et al.* (2007) Travel and venous thrombosis: a systematic review. *J Intern Med* **262**: 615–634.
14. Chandra D *et al.* (2009) Meta-analysis: travel and risk for venous thromboembolism. *Ann Intern Med* **151**: 180–190.
15. Oger E (2000) Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Group d'Etude de la Thrombose de Bretagne Occidentale. *Thromb Haemost* **83**: 657–666.
16. Clarke MJ *et al.* (2006) Compression stockings for preventing deep vein thrombosis in airline passengers. *Cochrane Database Sys. Rev* (2): CD004002.
17. Hsieh HF and Lee FP (2005) Graduated compression stockings as prophylaxis for flight-related venous thrombosis: systematic literature review. *J Adv Nurs* **51**: 83–98.
18. Burnett JC (2006) Long- and short-haul travel by air: issues for people with diabetes on insulin. *J Travel Med* **13**: 255–260.
19. Guerrant RL *et al.* (2003) Cholera, diarrhea, and oral rehydration therapy: triumph and indictment. *Clin Infect Dis* **37**: 398–405.
20. Haider R *et al.* (1994) Management of acute diarrhea in diabetic patients using oral rehydration solutions containing glucose, rice or glycine. *Br Med J* **308**: 624–626.
21. Burchard GD *et al.* (2009) Expert opinion on vaccination of travellers against Japanese encephalitis. *J Travel Med* **16**: 204–216.
22. Belsky DS *et al.* (1994) Case report: diabetes mellitus as a predisposing factor in the development of pyomyositis. *Am J Med Sci* **308**: 251–254.
23. Woods DE *et al.* (1993) Interactions of insulin with *Pseudomonas pseudomallei*. *Infect Immun* **61**: 4045–4050.
24. Sane T *et al.* (1990) Adjustment of insulin doses of diabetic patients during long distance flights. *Br Med J* **301**: 421–422.
25. Anon (2009) Rapid-acting insulin analogs. *Med Lett* **51**: 1327–1328.
26. Rosetti P *et al.* (2008) Superiority of insulin analogues versus human insulin in the treatment of diabetes mellitus. *Arch Physiol Biochem* **114**: 3–10.
27. Singh SR *et al.* (2009) Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *Can Med Assoc J* **180**: 385–397.
28. Vijan S (2010) Type 2 diabetes. *Ann Intern Med* **152**: ITC3 1–15.
29. Moore K *et al.* (2001) Extreme altitude mountaineering and type 1 diabetes: the Diabetes Federation of Ireland Kilimanjaro expedition. *Diabet Med* **18**: 749–755.
30. Moore K *et al.* (2001) Diabetes and extreme altitude mountaineering. *Br J Sports Med* **35**: 83.
31. Prociv P (1995) Deaths of Australian travellers overseas. *Med J Aust* **163**: 27–30.
32. Cummins RO and Schubach JA (1989) Frequency and types of medical emergencies among commercial air travellers. *JAMA: J Am Med Assoc* **261**: 1295–1299.
33. Cummins RO *et al.* (1988) In-flight deaths during commercial air travel. How big is the problem? *JAMA: J Am Med Assoc* **259**: 1983–1988.
34. Gong H (1992) Air travel and oxygen therapy in cardiopulmonary patients. *Chest* **101**: 1104–1113.
35. Luks AM (2009) Do lung disease patients need supplemental oxygen at high altitude? *High Alt Med Biol* **10**: 321–327.
36. Akero A *et al.* (2005) Hypoxemia in chronic obstructive pulmonary disease patients during commercial flight. *Eur Respir J* **25**: 725–730.
37. Fischer R *et al.* (2005) Lung function in adults with cystic fibrosis at altitude: impact on air travel. *Eur Respir J* **25**: 718–725.
38. Dillard TA *et al.* (1991) Air travel in patients with chronic obstructive pulmonary disease. *Arch Intern Med* **151**: 1793–1795.
39. Gong H *et al.* (1984) Hypoxia-altitude simulation test. Evaluation of patients with chronic airway obstruction. *Am Rev Respir Dis* **130**: 980–986.
40. Kelly PT *et al.* (2008) Air travel hypoxemia vs the hypoxia inhalation test in passengers with COPD. *Chest* **133**: 920–926.
41. Dine CJ and Dreider ME (2008) Hypoxia altitude simulation test. *Chest* **133**: 1002–1005.
42. Dillard TA *et al.* (1989) Hypoxemia during air travel in patients with chronic obstructive pulmonary disease. *Ann Intern Med* **111**: 362–367.
43. Conlon CP (2000) Travel and the immunocompromised host. *Hosp Med* **61**: 167–170.
44. El Sayed NM *et al.* (2000) Epidemic transmission of human immunodeficiency virus in renal dialysis centers in Egypt. *J Infect Dis* **181**: 91–97.
45. Parsons D *et al.* (2008) Travel-associated acquisition of hepatitis C – implications for the renal transplant waiting list. *Nephrol Dial Transplant* **23**: 2104.
46. Vedio AB *et al.* (2009) Hepatitis C, a hazard for haemodialysis patients during international travel. *J Infect* **58**: 392–393.
47. Bhattacharya S *et al.* (2009) Holiday haemodialysis and imported hepatitis C virus infection: a series of sixteen cases in two large haemodialysis units. *J Clin Virol* **45**: 296–299.
48. Nassar NN *et al.* (1998) Keeping travellers healthy. *Am J Med Sci* **315**: 327–336.
49. Almeida Mdo R *et al.* (2007) Epilepsy and recreational scuba diving: an absolute contraindication or can there be exceptions? A call for discussion. *Epilepsia* **48**: 851–858.
50. Dietz TE and McKiel VH (2000) Transient high altitude expressive aphasia. *High Alt Med Biol* **1**: 207–211.
51. Zrinzo LU *et al.* (2006) Commercial flight and patients with intracranial mass lesions: a caveat. Report of two cases. *J Neurosurg* **105**: 627–630.
52. Donovan DJ *et al.* (2008) Aeromedical evacuation of patients with pneumocephalus: outcomes in 21 cases. *Aviat Space Environ Med* **79**: 30–35.

53. Bagshaw M and Nicolls DJ (2008) Aircraft cabin environment. *Travel Med* **9**: 447–461.
54. Bagshaw M (2003) Air Transport Medicine Committee, Aerospace Medical Association. Medical guidelines for air travel. *Aviat Space Environ Med* **75**: A1–A19.
55. Shlim DR *et al.* (1991) Suddenly symptomatic brain tumors at altitude. *Ann Emerg Med* **20**: 315–316.
56. Seth R *et al.* (2009) Fitness to fly post craniotomy – a survey of medical advice from long-haul airline carriers. *Br J Neurosurg* **23**: 184–187.
57. DuPont H (2008) President's address: travel medicine and principles of safe travel. *Trans Am Clin Climatol Assoc* **119**: 1–27.
58. Suhner A *et al.* (2001) Effectiveness and tolerability of melatonin and zolpidem for the alleviation of jet lag. *Aviat Space Environ Med* **72**: 638–646.
59. Herxheimer A and Petrie KJ (2002) Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev* (2): CD001520.
60. Suhner A *et al.* (1998) Comparative study to determine the optimal melatonin dosage form for the allevation of jet lag. *Chronobiol Int* **15**: 655–666.
61. Morgenthaler TI *et al.* (2007) Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. *Sleep* **30**: 1445–1459.
62. Honigman B *et al.* (1993) Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med* **118**: 587–592.
63. Roach RC *et al.* (1995) How well do older persons tolerate moderate altitude? *West J Med* **162**: 32–36.
64. Veltri JC *et al.* (1994) Retrospective analysis of calls to poison control centers resulting from exposure to the insect repellent N,N-diethyl-m-toluamide (DEET) from 1985–1989. *J Toxicol Clin Toxicol* **32**: 1–16.
65. Fradin MS (1998) Mosquitoes and mosquito repellents: a clinician's guide. *Ann Intern Med* **128**: 931–940.
66. Castelli F *et al.* (1996) Age-specific antihepatitis A virus seroepidemiology in Italian travellers: indications for anti-hepatitis A vaccination. *J Travel Med* **3**: 214–218.
67. Schwartz E and Raveh D (1998) The prevalence of hepatitis A antibodies among Israeli travellers and the economic feasibility of screening before vaccination. *Intern J Epidemiol* **27**: 118–120.
68. Lindsey NP *et al.* (2008) Adverse event reports following yellow fever vaccinations. *Vaccine* **26**: 6077–6082.

Chapter 28 Aid workers, expatriates and travel

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Introduction

In this chapter we will discuss aid workers and expatriates. We use the term 'aid workers' as an abbreviation for relief and development workers, who usually work with international non-government organisations (INGOs). In 2000, there were an estimated 37,000 INGOs, and approximately 19 million INGO workers [1].

Expatriate, derived from the Latin verb expatriare, is made up from two words: ex, meaning 'out', and patria, which means 'native country'. We use this term to refer to individuals who move away from their native country to accomplish a job-related goal. Data published by the Organisation for Economic Co-operation and Development (OECD) [2] indicate that globally there may be as many as 36 million expatriates, 17.5 million from OECD countries.

Expatriates are a very heterogeneous group. Assignments range from less than 3 months, to permanent contracts. Besides aid workers, expatriates include business people, diplomats, missionaries, explorers, geologists, researchers, miners, peace-keepers, journalists and people in the armed forces. An increasing number of expatriates come from countries in the 'global south'. In fact, 1.5 million expatriates from South Asia live in the United Arab Emirates alone; this constitutes 80% of Dubai's total population.

As diverse as the background are the health-related factors. While some enjoy ready access to sophisticated and well-funded medical care, others live in primitive settings with a minimum of support and struggle to access basic healthcare. Some expatriates, although isolated from amenities found in industrialised countries, live in a relatively simple, predictable and controlled environment. Others live and work in affluent environments with modern amenities, yet embark on risk-taking diversions throughout their sojourn.

As early as the 1890s mission societies were using medical screening to determine who was 'fit' for international assignments. At the same time, mortality from infectious diseases was so high that missionaries were instructed to pack their belongings in coffins. Malaria alone claimed the lives of 60% of missionaries in West Africa during the nineteenth century [3].

Added to this were losses from premature attrition related to psychosocial stress. In 1913, Price wrote a paper entitled 'Discussion on the Causes of Invaliding from the Tropics', documenting attrition rates of 40%, the majority (20.6%) 'invalid' because of nervous conditions of a neurasthaenia type [4]. Attempting to reduce the rate of premature attrition, many agencies established a health appraisal process that was intended to screen out candidates who might be ill suited for the challenge. In 1920, Culpin introduced psychological screening for employees of the Anglo-Persian oil company and reduced repatriation from 20% to 4% over 5 years. Later, others concluded that the efforts were often in vain [5].

Risk of illness among expatriates is influenced by a variety of factors that can be extrapolated from those identified among other travellers, including age, sex, behaviour, climate, environment and vulnerability to infectious diseases. However, the complexity of cross-cultural assignments and the varied physical and emotional responses to those challenges appears to predispose expatriates to ailments that are not shared by the short-term traveller [6]. In 1963, Useem coined the term 'binational third culture' to depict the culture that bridges the western culture to the host culture in the physical setting of a non-western society. The children became known as 'third culture kids' or TCKs in recognition of the transcendent culture that they shared with other children who spend or have spent a portion of their developmental years in a culture that was not their own.

Despite a longstanding acceptance of medical and psychological testing, there is relatively little modern published data to improve our understanding of the health risks of expatriates, especially data that would distinguish the physical

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health risks of this community from risks identified in the short-term traveller. However, there is ample data to demonstrate the impact of cross-cultural stress that adds to the diversity and complexity of international assignments. It has been estimated that 60% of all referrals for medical treatment in the Foreign Service have a stress-related basis; therefore it is prudent for healthcare providers to recognise the factors that could influence both the medical and psychological health status of expatriate personnel [7]. In fact the burden of suffering related to the psychosocial burden is more significant than that related to infectious diseases. Frequently, the medical and psychological dimensions are intertwined, making it mandatory to consider a multidisciplinary approach if care to enhance effectiveness is one of the goals of the healthcare professional. To that end, both disciplines will be addressed in concert throughout this chapter as the data on morbidity, screening, preparation, care during the international assignment and re-entry are examined.

Morbidity, attrition and mortality among expatriates

Expatriates are often at increased risk of illness and injury because of conditions and inadequate medical facilities in the areas in which they work, although studies documenting morbidity and mortality among expatriates are too limited to differentiate all of the risks experienced by different subsets. The Peace Corps developed a formal epidemiologic surveillance system in 1985 to monitor health trends in more than 5,500 volunteers. The most commonly reported health problems were diarrhoea (48 cases per 100 per year), injuries (20 cases per 100 per year) and skin conditions (19 cases per 100 per year). The surveillance data in Peace Corps volunteers 25 years earlier was comparable, although in that series respiratory illnesses were also significant (27 cases per 100 per year) [8].

Lange *et al.* [9] looked at morbidity of refugee relief workers in Somalia, Ethiopia and Malaysia. Thirty-eight staff serving the equivalent of 46 person-years reported a total of 49 health problems that resulted in time lost from service. Infectious diseases accounted for the majority of reported illnesses; 57% were related to food-borne agents. The infectious disease experience mirrored that of Peace Corps volunteers.

Humanitarian aid workers with the International Committee of the Red Cross (ICRC) participated in a study designed to determine health risks and risk-taking behaviour while on mission. Eighty-six per cent of 1,190 respondents judged that they were in excellent health when deployed; however, after completion of assignments, with a mean duration of 11 months, 36.4% reported that they were in worse health. The majority (72.8%) had at least one illness: diarrhoea (44%), fever (25.9%), fatigue (19.9%), dermatological conditions (16.3%) and dental problems (12.6%). Ten percent reported that the assignment was interrupted prematurely, 13.6% because of illness and 28.8% for personal reasons [10].

Prevalence of psychological problems among expatriates

Many describe their time overseas as enjoyable and fulfilling. Making new friends and job satisfaction are usually reported as the best part of the experience [11]. Nevertheless, expatriates as a group encounter a variety of potentially stressful experiences. Difficulties commonly reported include cross-cultural adjustment, loneliness, communication problems, unpredictable circumstances, role ambiguity, long working hours, little opportunity to relax or socialise, overwhelming responsibility, ethical dilemmas and powerlessness. In some countries there are extreme temperatures to contend with, and the living and working conditions may be uncomfortable or dangerous. Some expatriates encounter wide-scale poverty, injustice, suffering, despair and death. Risks of being caught up in warfare, terrorist attacks, kidnapping or other criminal activities appear to have increased in recent years. Many expatriates do not have access to any form of psychological support.

In guidelines produced by the ICRC, it is stated that: 'Cumulative stress . . . affects health personnel and humanitarian workers in particular, as they always have to perform in overwhelming situations, where the demands are such that they can never be met.' [12]

Expatriates tend to have high ideals and expectations, which may put them at particular risk of experiencing emotional exhaustion or 'burnout'. [13, 14] They tend to work very long hours, perhaps because they feel guilty about taking time off when the needs are great, or because they feel that there is little to do in their new environment apart from work. In one study of 200 aid workers, 50% claimed they regularly worked more than 60 hours a week. One respondent said that, in retrospect, 'more breaks and less work would have been more efficient, as we were all burnt out' [15].

Given the magnitude of stressors that expatriates may experience, and the lack of help received in coping with these, one might expect to find psychological difficulties among this group. Clinical observation and surveys have supported this hypothesis [16–18]. In a survey of 390 missionaries, Parshall [19] found that 97% reported experiencing tension,

88% found anger to be a frequent or occasional problem, and 20% had taken tranquillisers since becoming missionaries. Donovan [20] stated that 25% of missionaries return home prematurely and 50% were likely to work with reduced efficiency because of stress.

Depression is probably the most common form of psychopathology found among expatriates [11, 14]. Clinicians have suggested that other common reactions include anxiety disorders (including post-traumatic stress disorder, PTSD), drug/alcohol abuse, loss of self-esteem, anger problems, chronic fatigue syndrome and psychosomatic problems [14, 18, 20–22].

A few empirical studies have been conducted on the psychological adjustment of expatriates. In a longitudinal study, Paton and Purvis [23] administered the General Health Questionnaire (GHQ-30) [24] to a group of 18 nurses before they went to work in Romanian orphanages for 3 months, and again on their return. The nurses were also administered the Impact of Event Scale (IES) [25] on their return. GHQ-30 scores increased significantly during the time in Romania, indicating an increase in health-related problems. On the IES, the nurses reported symptoms of intrusive thoughts and avoidance that resembled those of clinical trauma patients. These symptoms were maintained at 1-month follow-up. In addition, 56% of the nurses reported that they had experienced depression (although this probably indicated low mood rather than clinical depression), and 22% reported sleeping difficulties.

Paton [26] also found high levels of symptomatology among relief workers in El Salvador, Armenia, Iran and the Philippines. Among those who had worked in Armenia, 75% reported depression.

In another study [11], aid workers representing 62 different organisations completed questionnaires after returning to their home country. Participants were recruited randomly, and the response rate was remarkably high (82%), with 145 individuals completing the questionnaires. The mean time spent as expatriates was 51 months, although there was a wide range. Forty-six per cent of these respondents reported that they had experienced a psychological illness of clinical severity, either while they were away or on their return home. In 87% of cases the primary diagnosis was depression, with another 7% having been clinically diagnosed as having chronic fatigue syndrome, 4% PTSD and 2% other diagnoses. These figures were based on self-report of clinical diagnoses, but as the responses were anonymous and the sample appeared to be reasonably representative, there is no particular reason to doubt these figures.

In Lovell's study [11], expatriates who reported psychological problems were found to have spent significantly longer overseas than those who did not report such problems. This suggests that it might be worth considering shorter contracts (e.g. for 3 years) for expatriates, so that there would be less time for stress to accumulate and readjustment on return might be easier. Contracts could be renewed after psychological reassessment for those who wished to continue the work. Other studies have found that aid workers are most at risk of psychological difficulties while on their first assignment or if they have had more than five previous assignments [27, 28].

Another issue raised by Lovell [11] was that sending agencies were only aware of about one in six of the cases of psychological difficulties among their workers. Many workers chose not to disclose their difficulties to their organisation as they feared that this would interfere with their chances of going overseas again, or of getting promotion or a good reference for another job.

Premature attrition

Premature attrition was addressed as early as the 1920s and continues to be a major concern. The published data from a global survey conducted among missionary personnel indicate an attrition rate of 3–8% per year in larger organisations, and up to 60% in agencies that have fewer than 10 employees [29]. Health reasons are cited as the most common of the personal reasons for attrition, although the stated reason may not always correspond to the real reason. Not all expatriates are aid workers. Although there has been little research on the mental health of other groups of expatriates, Deshpande and Viswesvaran [30] stated that an average of 20–40% of all expatriate managers returned home early due to poor performance or an inability to adjust to the new culture. Moreover, nearly half of those who did not return early were reported to function below their normal level of productivity.

Harzing [31] questioned the high expatriate failure rates that had been reported, stating that there had been few reliable large-scale studies. Perhaps the figures have been exaggerated, but it certainly seems clear that the vast majority of American multinational companies see more than 10% of their expatriates return home prematurely [32]. The rate may be much higher among expatriates sent to the countries that are culturally the most different from their home country.

Mortality data

Studies have found the mortality rate to be doubled among aid and development workers compared with colleagues remaining at home, despite medical selection of healthy

applicants for aid work [33]. In contrast, the adjusted rate among missionary personnel was 40% lower than would be expected in a comparable US population, although mortality risks from homicides and complications of pregnancy were greater [34]. Suicide emerged as significant in Peace Corps personnel, accounting for 13% of reported deaths compared with <1% among missionary personnel. Both North American missionaries and Peace Corps personnel were at greatest risk from motor vehicle accidents, with motorcycles accounting for a disproportionate number of deaths [34, 35]. From 1970 to 1985, the rate of death from infectious diseases approximated that reported in the US; this may change now that HIV exposure has been found to be an occupational risk for aid workers in some parts of the world [33]. Deaths due to violent attacks or warfare appear to have risen in recent years [36].

Pre-departure assessment

Purpose of pre-departure screening

Premature attrition is costly; thus, at a very basic level, pre-departure screening could be viewed as a way of protecting that investment, hoping to avert unnecessary premature attrition. However, like alchemists of old, the quest for a universal screening tool that would predict success has ended in frustration. Legal constraints in many countries prevent employment discrimination based on physical impairment, whereas the laws of host cultures often impose medical restrictions for employment visas. Environmental, climactic and political upheaval could pose other threats that would eliminate some applicants.

Ultimately, from an ethical perspective, one could propose that a thorough health assessment provides baseline data on which care and health management strategies are founded. The 'Code of Good Practice' established by aid agencies in the UK asserts that the aid worker is the agency's most valuable resource and thus those who ascribe to this code affirm their commitment to maintain and enhance the wellbeing of their international employees [37].

Medical assessment

Morbidity and Mortality Weekly Report (MMWR) published a series on 10 'Great Public Health Achievements' in the 20th century [38]. Five are germane to expatriate health: vaccination, safer and healthier foods, control of infectious diseases, motor vehicle safety and safer work places. For expatriates, the risk appraisal and health management components of a medical assessment will intersect with five disciplines of medicine: public health, travel medicine, primary care, infectious disease and occupational health. Occupational health considerations that pertain to specific industries are beyond the scope of this chapter.

General assessment

Evidenced-based medicine has shaped our current understanding of the role and relevance of the periodic health evaluation (PHE). A meta-analysis of 21 studies published between 1973 and 2004 determined that the PHE improves delivery of some recommended preventive services and may lessen patient worry [39]. However, a sample of primary care clinicians revealed that goals set in Healthy People 2010 have not been realised in the general population [40, 41]. Further study demonstrated that persons with a personal primary care provider are significantly more likely to receive guideline-consistent care [42, 43].

Expatriates often sever ties with their primary care provider, thereby reducing the probability that they will receive guideline-consistent care unless other provisions are made. T. L. Dwelle (personal communication, 1996) evaluated the files of 204 missionaries who were assigned to an international setting and determined that 88% of the records did not have evidence to confirm that the applicant had been appropriately screened for cancer in accordance to the US guidelines.

Few conditions absolutely contraindicate a cross-cultural, international assignment, particularly if a person is medically stable. Self-selection will limit some applications when obvious impairments preclude international placement. However, although applicants could assume that they are medically stable, they could have pre-existing health problems that might be exacerbated by environmental conditions or other geographic specific risks. They could have asymptomatic disease, and treatment prior to departure might reduce risk and improve wellbeing.

Comprehensive health histories, arguably the most valuable component of a health assessment, have been designed to provide a consolidated history that facilitates the provision of guideline-consistent care. Furthermore, from a qualitative perspective, a structured questionnaire will serve to reduce inconsistencies based on external constraints. When complete, a health assessment should:

- delineate current health issues that require attention prior to deployment
- identify long-term problems where management issues are significant and could jeopardise the wellbeing of the individual or compromise the assignment
- determine the risk factors that could predispose an individual to developing certain conditions during the tenure of service

• promote adherence to appropriate preventive health guidelines, including recommendations for vaccine preventable diseases, malaria prophylaxis and other conditions known to be common in expatriates, including sexually transmitted infections.

Outcome of the medical assessment

After being appraised of the risks, the applicant and the management team may re-evaluate their options. For example, an aid worker with reactive airway disease might have applied for an assignment in a remote region where access to pharmaceuticals is limited and houses are heated with a low-grade coal. The history reveals that chemical irritants trigger their reactive airway disease. Understanding those risks, the employee might reconsider their placement, or the agency's management team could develop contingency plans in the event that this condition deteriorates.

Selective interventions

Selective interventions are services offered to asymptomatic persons with one or more risk factors for a target condition when treatment at a pre-clinical stage offers a better outcome than waiting until after the disease manifests itself [44]. Pulmonary function tests would clearly be justified for the individual noted above because the findings will further clarify the risk, which in turn could impact decisions made by the applicant and management team.

Appropriate selective interventions for other target conditions, such as diabetes mellitus, coronary artery disease, some types of cancer, osteoporosis and sexually transmitted infections, should be recommended in accordance to the standard of care in the applicant's country of origin. Understandably, national guidelines will vary.

Diagnostic imaging and laboratory testing should focus on age- and gender-specific risk factors. The outcome of these evaluations could prompt a need for more selective interventions.

There is a danger that equivocal findings could be overlooked in expatriates who will be living in a remote setting where follow-up testing is both costly and disruptive. Reports from diagnostic imaging are classical. When a report concludes that a follow-up examination is necessary in 6 months time, consideration must be given to the level of medical services in the host community. Should this prove to be limited, one is compelled to investigate further until the diagnosis is clarified.

When complete, the medical assessment apprises the applicant of their health risks while promoting guideline-consistent care, ensuring all primary, secondary and tertiary preventive measures have been considered. Placement, services and logistical support are important considerations for expatriate personnel employed by an agency. If chronic conditions exist, expedite the transfer of care to appropriate healthcare providers in the host country.

Psychological assessment

What sort of person would apply for a job far from family and friends, leaving the comfort of home, their belongings and all that is familiar, to work in a place where they would have to learn new skills, customs and maybe even a language, perhaps in an extreme climate?

Paluszny and Zrull [45] studied 50 applicants for missionary service. They found that, although the majority appeared to be well adjusted, seven (14%) had significant psychological difficulties. One anonymous aid organisation admitted in a survey that: 'Some situations require people who can destroy themselves and thrive on chaos . . . at times we have employed workaholics and alcoholics.' [46]

A small proportion of the people who apply to go overseas as aid workers or expatriates do so because of emotional difficulties, perhaps being motivated by guilt or a desire to escape from their current situation. The vast majority, on the other hand, are psychologically healthy [11]. Among those with no current difficulties, some are more vulnerable than others to experiencing difficulty in adjusting to the demands of the new culture. Those who cannot work effectively in the new culture may suffer from a loss of self-esteem and from stress-related problems. They may have to return home early, which can cause family problems and career difficulties. Their colleagues may also be adversely affected. Recruiting people for positions overseas, training them and transporting them abroad is a costly business. Difficulties carry a financial cost, as well as an emotional one. Moreover, if an organisation is perceived as having inadequate selection or support procedures, they may in future be refused entry visas or funding [47].

In an attempt to reduce such problems, many organisations now include psychological screening in the selection process. Researchers have generated long lists of qualities that are desirable among expatriates, which have been summarised as follows:

> He should have the stamina of an Olympic runner, the mental agility of an Einstein, the conversational skill of a professor of languages, the detachment of a judge, the tact of a diplomat, and the perseverance of an Egyptian pyramid builder . . . he should also have a feeling for culture; his moral judgment should not be too rigid, he should be able to merge with the local environment with a chameleon-like ease; and he should show no signs of prejudice [48].

Given that no one could possibly meet all these criteria, what type of psychological screening will provide the most useful predictive information about how the individual will adjust, cope and perform overseas?

Psychometric tests

It is rare for an expatriate assignment to 'fail' due to lack of skill or ability; 80% of 'failed' assignments are due to adjustment difficulties [49]. Therefore, the focus here will be on tests that help to assess the presence and severity of psychological difficulties, and measures that give an indication of personality characteristics, as these may help to predict adjustment.

There are three main advantages of psychometric testing. First, the candidate's score can be compared with standardised scores; therefore a test score may be perceived as more objective than a judgement based on 'intuition' during an interview. Second, test results may pick up indications of, for example, a personality disorder that might not have been apparent during an interview. The third advantage is that some psychometric tests are cost-effective, especially if they can be sent to the candidate for completion and scored relatively quickly. A major disadvantage is that tests can provide a false sense of security. Many factors interact to influence how an expatriate will adjust and perform overseas, and no single test measures all of these factors.

Little research has been conducted on the effectiveness of psychometric tests for predicting expatriate adjustment. The limited research that has been published has mainly concerned the use of the Minnesota Multiphasic Personality Inventory (MMPI, and the revised version MMPI-2) [50]. The MMPI was originally developed to diagnose psychological disorders, but has been revised and standardised on normal populations, and has been used effectively in some areas of personnel selection [51]. The MMPI has been described as 'the "gold standard" for detection of personality disorders' [52]. It also provides a broad range of information about other psychological disorders, and normal personality traits. Norms exist for people of different backgrounds and cultures [53]. Although computer programs are available to assist in the rapid scoring of responses, someone who has appropriate training and expertise should interpret the results.

Research suggests that the MMPI has some use in the prediction of expatriate adjustment [54–58]. Schubert and Ganter [58] conducted a double-blind study of 129 missionary candidates (or couples). They concluded that the MMPI was inadequate as a sole instrument in evaluating candidates, but had a high potential for use in combination with an in-depth psychological interview. Schubert stated: 'The MMPI allows insight into unconscious issues . . . and vulnerable underlying personality traits not apparent in clinical interviews alone . . . [Certain subscales] appear to tap some unconscious aspects of personality which are helpful in cross-cultural predictions' [59]. Schubert's research was based on the original MMPI, and not the MMPI-2. There are advantages and disadvantages to using each of these measures [51, 59, 60].

Despite the attention paid to the MMPI, it is not necessarily the most appropriate measure. It is important to choose a test that is not only reliable, valid and standardized, but will also answer the questions of interest. A test that is useful for one type of post may be of little value for another position [61]. Some people want a test that can help screen out applicants with psychological disorders, while others are interested in one that could help to identify strengths and weaknesses, or interests and values. The latter can assist in deciding where an individual will best be placed, in terms of both location and role.

Ones and Viswesvaran [62] reviewed the literature on personality-related predictors of expatriate 'success', and recommended that the 'big five' dimensions of personality (emotional stability, extraversion, openness to experience, agreeableness and conscientiousness) should be considered. A number of questionnaires consider such dimensions. Discussion with a psychologist can assist in ascertaining which test is most appropriate for a particular organisation.

It is not difficult for intelligent candidates to modify their responses to hide symptoms of depression or other difficulties, and even the validity scales of the MMPI-2, which are sensitive to global deception or defensiveness, can miss subtle 'toning down' of responses [63]. Therefore personality questionnaires obtained by job applicants may have low predictive validity [64, 65].

One strategy for addressing this is to use a questionnaire that involves a number of comparisons between equally desirable personality descriptions (e.g. 'Are you a hard worker or a creative thinker?'). Hirsh and Peterson [66] have developed such a questionnaire, based on the 'big five' personality dimensions, which appears to be more resistant to bias than Likert-type scales.

It is important that psychological tests, if used, are taken in combination with a clinical interview. The interview may uncover difficulties that were not apparent from questionnaire scores. In cases where the questionnaire results appear abnormal, the interview provides an opportunity to assess why. It is possible that an unusual profile is a sign of creativity or cultural difference, rather than psychopathology.

Selection techniques vary substantially across cultures [67]. Psychometric tests are of greatest use if they are appropriate for the applicant's culture, selected carefully to answer specific questions, interpreted skilfully and used in combination with a psychological interview.

Psychological assessment interview

It is recommended that every applicant for an expatriate post receives an in-depth psychological assessment interview. Ideally, a psychiatrist or clinical psychologist, who is able to assess the candidate's mental state, should conduct this interview. A skilled interviewer should be able to put the candidate at ease and elicit honest responses, or at least detect when a candidate is being defensive or dishonest. The manner in which people speak about their experiences, and what they choose not to say, can be just as important as what they say. The psychological interview generally lasts at least 2 hours, with the interviewer seeking to get to know the candidate as well as they can within this time.

The interview should include a life history covering the candidate's childhood and adolescence, and education and employment up to the present. The interviewer should attempt to build up a picture of the candidate's strengths and weaknesses. It is important to consider what causes candidates stress and how they handle it; how they deal with anger and frustration; how resilient, resourceful and flexible they are; and where they get their support from. Their motivation for applying for a post overseas should be explored, and interviewers should assess how realistic their expectations are, and discuss any previous experience of working overseas. As interpersonal problems are a major cause of stress and possibly of premature return home [11, 68], it is also important to assess how they relate to other people. The interviewer should also take a detailed history of any experience of traumatic incidents (including abuse), and any personal or family history of psychological problems. Where there is a vulnerability to psychological disorders, this should be carefully assessed. Foyle *et al*. [69] found that affective disorders among expatriates were associated with a past personal history of depressed mood, and a family psychiatric history. They concluded (p. 282):

> *Those with heavily loaded family and personal psychiatric histories should not be accepted for overseas service unless there is clear evidence that they have remained well for several years, have a good work record in their home country, and have shown a capacity for coping in general, and for maintaining good interpersonal relationships. There must also be good personal and medical support in the locations to which they will go* (italics in original).

A psychological assessment can be used not only to say 'yes' or 'no', but to provide recommendations that will help to maximise the probability that the candidate will adjust well. Knowledge of vulnerabilities can highlight any special support that might be beneficial. In some cases it is wise to advise delaying overseas work until there has been time to engage in personal or marital therapy. It may also be advisable to recommend a delay if the candidate has suffered from a recent bereavement or relationship breakdown.

If a couple will be moving overseas together, the individual partners should be interviewed separately, even if only one of them will be working. One of the predictors of an expatriate's adjustment is the spouse's adjustment [70], and there is a strong relationship between marital satisfaction and depression among expatriate couples [71]. If the couple have children, it is useful to assess the whole family. Concern about children is a common cause of early return, and potential problems might be identified during the assessment, avoiding much distress later [72].

The effectiveness of a psychological interview depends to a large extent on the skill and experience of the interviewer. Fisher *et al*. [73] found that assessment ratings made by more experienced psychiatrists correlated significantly and positively with the later performance of Peace Corps volunteers, while the ratings of less experienced interviewers did not. Likewise, Gunderson and Kapfer [74] found that the psychological interview had a weak predictive validity when the interviewer was poorly informed about the placement environment, but better predictions were made when interviewers were provided with more information.

Even if the applicant has worked overseas previously, there should be a brief reassessment before every new assignment. It is not rare for applicants with psychiatric disorders to be accepted for reassignments without further psychological screening, to the detriment of themselves and those who have to support them in their post [11].

Other forms of psychological assessment

Some agencies use simulation activities as part of their assessment [47]. Some organisations inform candidates that their entire period of training is a prolonged assessment period. Additional assessment such as this may have value, but as yet research on such activities is lacking, and so they should only be used in addition to a psychological interview, and not in place of one.

Conclusions concerning psychological assessment

It is recommended that a psychological assessment interview should be part of the selection procedure for every assignment and reassignment. The interviewer should have some knowledge of expatriate life and the relevant environment. A major purpose of the interview is to check whether the candidate is currently suffering from any psychological disorder and to assess areas of vulnerability. If more detailed information is desired, a carefully selected psychometric test might provide this.

Pre-departure: preparation

Many of the guidelines for pre-departure preparation will also apply to the short-term traveller and thus will be dealt with in more detail in other chapters. Suffice it to say that one cannot assume that the organisation's guidelines will be in accordance with current standards of care [43], nor can one assume that the person will adhere to the counsel provided. Although 97% of the expatriates deployed by the ICRC were counselled regarding malaria prophylaxis, only one-third adhered to those guidelines [10]. Adherence to recommendations appears to decrease over time, although persons over the age of 50 were less inclined towards risk-taking behaviour when compared with younger counterparts [75].

Immunisations

Immunisation advice is thoroughly addressed elsewhere; however, there are some risk factors that are particularly significant for the expatriate community and they will be briefly addressed here.

Hepatitis B

Hepatitis B is an established risk for expatriates. This partly results from unprotected intercourse in non-monogamous relationships, and partly from inadvertent exposure in communities where the prevalence of hepatitis B is high. A recent World Health Organization (WHO) study showed that up to 75% of injections for healthcare purposes in developing countries are given with unsterile equipment [76].

Given the potential for adverse outcomes, the efficacy of the vaccine and the relatively low cost, universal immunisation for the expatriate task force can readily be justified [77, 78].

Japanese encephalitis B

Japanese encephalitis B vaccine previously had the potential to harm the recipient. However, a new cell culture vaccine has been shown to be safe and equally immunogenic. Clinical disease is associated with a mortality rate ranging from 10 to 25%, with up to 50% of survivors demonstrating permanent psychoneurological sequelae [79]. Although persons in urban settings are usually exempt, one should determine if the cumulative risk could exceed 4 weeks during the proposed assignment [80]. The new cell culture vaccine is approved for persons 18 years of age or older, which may be an issue for expatriates with family in high-risk settings [81].

Rabies

It is difficult to assess the risk of exposure to rabies but the rate of post-exposure treatment closely approximates 1 per 1,000 volunteers per month among expatriates living in rabies enzootic regions [82–86]. The risk of children being bitten is conservatively estimated to be four times greater than that of adults [86]. Furthermore, bites in children are usually higher on the trunk or face and are more severe or, conversely, minimised and neglected.

Dogs are usually the source of risk. Often pets are involved. It is disturbing to note that many expatriates keep pets that are not appropriately vaccinated against rabies. Post-exposure treatments are often delayed, biologics may not be available in less affluent countries and frequently management is not in accordance to WHO guidelines [82].

Persons relying exclusively on post-exposure prophylaxis (PEP) following a bite or scratch require rabies immune globulin (RIG, often unavailable in developing countries) plus four [87] doses of a potent tissue culture vaccine. For post-exposure vaccination to work and be cost-effective, it is essential that medical expertise be available on an urgent basis and that there be access to potent tissue culture vaccines plus RIG or purified equine RIG.

Expatriates residing in rabies enzootic countries with limited access to rabies biologics, particularly RIG, should consider pre-exposure immunisation. A prior history of post-exposure prophylaxis or pre-exposure immunisation with a tissue culture vaccine on days 0, 7, 21 or 28 will obviate the need for RIG post-exposure [88]. Pre-exposure immunisation does not eliminate the need for careful wound management and persons with category II or category III wounds still require two additional doses of a tissue culture vaccine on days 0 and 3.

Given that rabies prevention for persons previously immunised with a cell culture vaccine relies on the anamnestic response to the two post-exposure doses of the vaccine, routine booster doses are not required for expatriates unless there is judged to be a significant risk for inapparent exposure, or there is a likelihood that access to care will be limited so as to prevent timely administration of the post-exposure doses. Persons at risk for inapparent exposure must follow the usual guidelines for serological testing and booster doses [87, 88].

Cholera

Routine immunisation against cholera is not recommended; however, the oral cholera vaccine effectively reduces the volume of fluid loss and therefore is recommended for persons residing in endemic areas where access to rehydration therapy may be limited [89].

Tick-borne encephalitis

In terms of aid workers and the military, tick-borne encephalitis vaccine is an important issue, given the need for ongoing aid and peacekeeping in the Balkans, and for long-term health and development programmes in Eastern Europe and in the endemic band, which runs across the former Soviet Union.

On balance, aid workers, expatriates, longer-term travellers and environmentalists should consider having this vaccine if spending significant time in rural settings, especially in forested areas in late spring and summer in pockets where the disease is known to exist [90].

Malaria

Risk factors

Malaria was the leading cause of death among expatriates who died from infectious diseases [34] and continues to pose a threat in sub-Saharan Africa, where the rate of malaria is at least 10-fold greater than in other malarious countries [91], with the exception of Papua New Guinea and Papua Indonesia [92]. The true incidence of malaria in expatriates is difficult to determine, but rough estimates range from 31 per 1,000 per year in Asia to 209 per 1,000 per year in West Africa [93–95]. The majority of diagnoses are based on the presence of fever or are diagnosed by laboratories where the false-positive rate could be as high as 75% [96, 97].

The risk of malaria appears to increase over time and compliance appears to decrease over time, particularly evident in persons who resided in malaria-endemic regions for 2–3 years or longer [91, 93, 98, 99]. In sub-Saharan Africa, children, persons who do not take antimalarial prophylaxis and persons living and working in rural areas are at increased risk of contracting malaria. Some environmental factors, such as altitudes above 2,000 m and arid climates, also mitigate malaria risk. There appears to be a lower risk in urban locations, even in countries with urban transmission [100].

Counterfeit malaria drugs increase the risk of failed prophylaxis and treatment. In response to this threat, the WHO set up a Prequalification Programme to assess the quality, safety and efficacy of medicinal products, and in addition, inspect manufacturing and clinical sites. The current list of WHO prequalified products and manufacturers (brand name and generic) can be seen on the WHO website at: http://apps.who.int/prequal/.

Chemoprophylaxis

Guidelines on the prevention of malaria in expatriates should not deviate significantly from standard guidelines (*see* Chapter 10). The lack of international consensus on chemoprophylaxis is problematic for the expatriate community. From the descriptive data available, it becomes evident that the practice guidelines may have little influence on the behaviour and practice of the expatriate and underscores the importance of meticulous advice when preparing expatriates who anticipate living in malaria-endemic regions [101].

Many would concede that mefloquine is the preferred antimalarial for chloroquine-resistant areas when convenience, cost and efficacy are the primary considerations. Failure of mefloquine prophylaxis is due primarily to noncompliance [96]. Studies on Peace Corps volunteers have demonstrated that mefloquine is safe and well tolerated by most individuals who have continued to use it over extended periods of time [102–104]. However, mefloquine has the highest incidence of adverse events compared with other prophylactic agents [105]. In a study that involved 1,200 persons from a broader sector of the expatriate community working in sub-Saharan Africa, only 3% continued to use mefloquine, primarily because of concerns regarding neuropsychiatric side effects. Of those who were initially prescribed mefloquine, 28% noted that colleagues or health workers influenced them to change; 20% changed to another prophylaxis regimen because of side effects, although only half of those were classified as neuropsychiatric in nature [93].

Chloroquine and proguanil resistance is known to be widespread throughout sub-Saharan Africa, yet it was found to be the favoured antimalarial regimen for 55% of the persons included in this large cross-section of expatriate workers. Chloroquine alone or proguanil alone was utilised by about 20% in this 1998 study [93].

Maloprim, a combination of dapsone and pyrimethamine, or pyrimethamine alone was the choice for another 20%. A Canadian missionary in Malawi, using dapsone and pyrimethamine for malaria prophylaxis, died in 1999 from complications related to malaria, underscoring concerns regarding resistance [106]. Agranulocytosis developed in 1:2,000 when the dose of dapsone and pyrimethamine was increased to improve efficacy [107]. Doxycycline has been recommended as an alternative to mefloquine, yet it is not widely utilised by members of this community, in part because of concerns regarding safety and tolerance. However, tetracycline derivatives have been utilised for long-term treatment of other disorders such as acne.

Safety

Although there are few studies on the safety of the long-term use of antimalarials, in general all recommended drugs for chloroquine-resistant malaria have been found to be safe:

mefloquine in Peace Corps volunteers for 2.5 years; doxycyline in Australian military; primaquine in Javanese transmigrants in Southeast Asia for 1 year; and atovaquone/proguanil post-marketing studies for 34 weeks. In the few areas that are endemic for chloroquine-sensitive malaria, expatriates have used chloroquine safely for many years. However, there may be a risk of chloroquine retinopathy when the drug has been used continuously for 5–6 years; the UK advisory committee on malaria prevention recommends eye examinations every 6–12 months after 6 years. Although no studies have addressed the safety of long-term use of repellents, reports of problems with long-term use have not been published [108]. The prevailing opinion by national expert committees is that the long-term use of antimalarials for prophylaxis is considered to be safe and important regardless of the duration of the stay in a malarious area [101].

Adherence

Adherence is generally poor [100]. As noted above, the choice of antimalarial medication does not necessarily conform to the standard guidelines. Furthermore, half of the study participants adjusted their regimen, independent of medical counsel, after their arrival. In sub-Saharan Africa only 75% of expatriates use regular chemoprophylaxis, in Asia about 28% and in the Pacific about 35%. Although personal protection measures have proven to be effective, only 38% of expatriates screened doors and windows, 53% used mosquito netting and only one in five participants treated their nets with insecticides [93].

Self-diagnosis and self-treatment

Self-diagnostic kits are now available and have proved to be very accurate and reliable in the hands of laboratory workers [109–111], but earlier studies demonstrated that they were less reliable in the hands of travellers [112, 113]. A more recent study suggested that self-diagnostic tests are a promising reliable diagnostic method for malaria in travellers [114].

Given that expatriates represent a reasonably finite group, training may prove to be efficient and effective. Self-diagnostic kits that require refrigeration will limit access to this technology in some regions.

Of the drugs available for self-treatment, the combination of atovaquone and proguanil appears to be the most promising: it is easy to administer, it is relatively well tolerated, it has no known severe adverse reactions and it has an efficacy rate close to 100% [115]. Pyrimethamine with sulfadoxine (Fansidar) is no longer an effective antimalarial agent in many parts of Southeast Asia, Africa and the Amazon region of South America. Halofantrine is still available in some international settings, although it is no longer recommended because of the potential for cardiac complications. The artemether derivatives are now widely available and are used by expatriates for self-treatment. The availability of artemether/lumefantrine (Coartem/Riamet) has made self-treatment with these derivatives easier and more reliable [116].

Malaria and pregnancy

There is an increased risk of severe malaria during pregnancy, which may result in maternal and neonatal death, miscarriage and stillbirth. Special care should be taken to avoid mosquito bites, and chemoprophylaxis should be used.

The use of doxycycline and primaquine are contraindicated in pregnancy. Chloroquine and proguanil are considered to be safe in pregnancy, although they are not as efficacious as mefloquine in preventing drug-resistant *Plasmodium falciparum* infection. Based on current data, mefloquine is also believed safe and should be considered the drug of first choice in regions where the attack rate and chloroquine resistance is high [117, 118]. Data on the safety of atovaquone proguanil is not yet complete enough to advise about its use in pregnancy.

Malaria prevention in children

With the exception of doxycycline, antimalarials, including primaquine, are safe for children when administered at the prescribed dose. Children and adolescents are at special risk of malaria, perhaps because of poor adherence or inaccurate calculation of the dose [91], and they may rapidly become seriously ill. Babies, including breast-fed infants, and children should be well protected against mosquito bites and receive malaria chemoprophylaxis. In the older literature, children appeared to be at greater risk than adults for *N*,*N*-diethyl-*m*-toluamide (DEFT) toxicity, which included seizures among other central nervous system abnormalities. However, in reality very few cases of DEET toxicity have been documented in children. Recently, the FDA and American Academy of Pediatrics have recommended the use of 30% DEET down to 2 months of age.

Tuberculosis

Tuberculosis is not only spreading, but the proportion of multidrug-resistant cases is rising, in some areas explosively. It is estimated that between the years 2000 and 2020, nearly 1 billion people will be newly infected and 70 million will die if control is not strengthened [119].

Many expatriates, particularly aid workers and missionaries, have a significant risk of tuberculosis. Risk factors include working in refugee camps, in long-term health and development, in urban health programmes and among communities that also have a high level of HIV disease. One prospective study of travellers showed that the risk of tuberculosis (mostly asymptomatic) was 3% per year of stay, whereas in healthcare workers it was almost twice as high [120].

Opinions differ as to the value of routine BCG immunisation for those who are tuberculin negative (Chapter 14). Studies suggest that current strains of BCG have been overattenuated and thus may be less effective than they were during earlier trials [121]. Current advice in the UK would be to offer BCG to previously unvaccinated, tuberculin-negative individuals according to the destination and the nature of travel. The vaccine is recommended for those under 16 years who are going to live or work for more than 3 months in a country where the annual incidence of TB is 40/100,000 or greater [122].

In North America, BCG is not recommended. Rather, the tuberculin skin test (TST) is administered to identify latent TB infection (LTBI) and Isonizide (INH) prophylaxis is offered to persons who convert to being skin test positive. Exceptions include travellers planning extended stays in areas of high TB incidence, particularly when a programme of serial TST and appropriate chemotherapy is not possible; persons with liver disease; persons with intolerance to INH; people in areas where the prevalence of drug resistance, particularly multidrug-resistant (MDR) TB, is high [123].

A pre-departure TST is recommended for persons who are residing in an area with a high incidence of TB and who have one or more of the following risks: a high level of risk for development of active TB, plans to travel or reside for 3 months or longer (particularly if the traveller is a child), and intention to participate in a high-risk activity (e.g. healthcare work, refugee care, missionary or other work that may involve exposure to the resident population).

A pre-travel two-step TST is recommended for individuals who are not candidates for treatment of LTBI unless recent conversion occurs, and individuals who will be entering a serial TST screening programme for occupational reasons [123]. Follow-up TB skin tests should be carried out 2 to 3 months after departure from an endemic area.

Persons with HIV disease should be discouraged from working in areas of high risk for TB.

Diarrhoeal diseases

Diarrhoeal diseases related to bacterial infections account for the majority of illnesses among expatriates [8]. There is both a seasonal variation and a significant variation from one region to another. Foods cooked earlier in the day, such as lasagna and quiche, as well as blended fruit and yogurt drinks have recently been identified as risk factors. Other dominant risk factors include younger age, shorter duration of stay and eating in restaurants. Although the severity of diarrhoea in expatriates may be somewhat less than that found among short-term travellers, the morbidity is still significant and remains so for up to 2 years [124, 125]. In Thailand, the risk of diarrhoea caused by *Campylobacter jejuni* appears to decrease after 1 year of residence [126].

Hand washing for household food handlers and employees should be emphasised in addition to standard advice regarding water purification and food precautions.

The expatriate families should be instructed in self-treatment protocols. In contrast to the short-term traveller, they should be familiar with the varied presentations and seasonality to ensure that the most appropriate regimen is applied to their situation.

Risk behaviour

Excessive alcohol consumption and a high rate of extramarital sexual activity are common among certain groups of expatriates [15, 127, 128]. In some cases these behaviours are related to peer pressure and expectations, while in other instances they are a consequence of stress, or an attempt to avoid unpleasant thoughts and feelings, or a result of loneliness and separation from the social support network (perhaps including the spouse). Boredom and a lack of opportunity for recreational activities may also be a factor. In many cases, expatriates do not use condoms during sexual activity [10, 128, 129], increasing the risk of HIV infection and other sexually transmitted diseases.

Sexually transmitted diseases

Sexually transmitted diseases have been associated with travellers since they were first described and are a well-documented risk in the expatriate community [130–133]. A study of approximately 900 Dutch expatriates living in four different geographic regions showed that 41% of males and 31% of females reported having sex with casual or steady local partners, and 11% of males and 24% of females acknowledged that they had casual or steady expatriate partners during an average stay of 26 months. Consistent condom use with steady local or expatriate partners was noted by 69% in these study participants, compared with 21% reported in an earlier study [133].

HIV

There is little doubt that human immunodeficiency virus (HIV) transmission is primarily related to sexual activity and

occupational hazards. Little is known about the incidence of HIV among aid and relief workers [134, 135]. Although extremely rare in some groups, Schouten and Bordoff [33] confirm that cases are occurring and Dutch medics in HIV endemic areas were found to have a mean occupational risk of HIV of 0.11% per person per year. Elsewhere, 1.1% of Belgian advisers working in Africa and 0.9% of European expatriates living in Africa were found to be HIV-positive in a voluntary screening programme [130]. Houweling and Coutinho [136] found that of 2,000 Dutch expatriates working in sub-Saharan Africa, 0.4% of men and 0.1% of women contracted HIV. One case related to occupational exposure. We can expect the number of reported cases to increase, given the explosive increase in HIV infection in many parts of the world where aid workers are posted and expatriates live [137].

Aid workers and expatriates may need pre-departure testing for visa applications, or to provide health counsel for management of unique health risks, especially as it pertains to opportunistic infections and live vaccines. Treatment should be offered to persons found to be HIV-positive.

There remains the vexed issue of post-exposure prophylaxis following an occupational health exposure (or sexual assault). Kits are increasingly available – made up in 7- or 28-day packs and comprising two or three antiretroviral drugs, commonly comprising zidovudine, lamivudine and a protease inhibitor such as lopinavir. These kits are largely designed for aid workers perceived to have a high occupational risk of HIV exposure, including doctors, nurses and medical students. An increasing number of agencies are now providing these kits. Detailed guidelines and instructions about the best ways of using these are currently being hammered out in the hopes that a degree of consensus will emerge. The area is fraught with medical, financial, logistical and moral issues. Some agencies, including Médecins sans Frontières, are following clearly defined and managed protocols [138].

Wider preparation

One essential in the preparation of the aid worker or long-term expatriate is for advice to be targeted to risk. Most illnesses will not be vaccine-preventable, but can be minimised by taking safety precautions specifically targeted to the destination, occupation, length of travel and perhaps above all to the personality of the traveller. The risk taker will usually be at greater danger and more difficult to counsel than the cautious. A study of expatriates with ICRC determined that persons over 50 years of age were less inclined towards risk-taking behaviour [10].

A travel health consultation taking at least 30 minutes is usually needed to adequately assess and address the health risks of long-term travellers. The emphasis will be on providing sound information on reducing risk, some applicable to all destinations such as accident prevention and food hygiene, others more specific, such as how to reduce the risk of dengue fever, bilharzia (shistosomiasis) or other locally important illnesses. Advice should be accompanied by simple, easy-to read handouts, an easily portable travel health manual and a list of websites or advice on how to subscribe to informed online health information for the international traveller.

Psychological training and preparation

Many people who show no particular signs of vulnerability at assessment go on to either develop difficulties while overseas or return home early because of stress [139, 140]. Can adequate training and preparation make a difference?

Tung [32] investigated why the rate of premature repatriation was more than twice as high among expatriates from the US compared with those from Europe or Japan. Tung found that American companies were much less likely than European or Japanese companies to provide formal training for cross-cultural posts.

Not all groups of American expatriates have a high attrition rate, and so the difference cannot be explained in terms cultural differences in expectations or attitudes. Henry [141] observed that only 3–4% of American Peace Corps volunteers were sent home early as 'out-and-out selection errors', compared with 30% of expatriates sent abroad by American companies. One of the major differences between the groups was the 3-month training course received by the Peace Corps volunteers.

Deshpande and Viswesvaran [30], in a meta-analysis of 21 studies, concluded that cross-cultural training had a strong and positive effect on cross-cultural adjustment, job performance and cross-cultural skills development. Holmes and Piker [49] estimated that expatriate attrition averaged around 40% among companies who neither screened candidates for cultural adaptability nor provided cultural orientation, compared with 25% among those with orientation programmes only, and 5–10% among those using both screening and orientation programmes.

A study of 600 mission agencies based in 22 countries, with almost 40,000 long-term cross-cultural missionaries, compared agencies with high attrition rates with those with low attrition rates. Among other findings, they report that high retaining agencies:

- use more psychological screening in selection
- require more pre-field training
- value, promote and facilitate continuous learning and development

• provide appropriate and significant re-entry preparation and debriefing opportunities
• dedicate more staff time and finances to staff care [142].

An important part of the preparation package should be to explain what to expect in terms of culture shock, and the longer-term adjustment process. It is not unusual for expatriates to have stress-related symptoms at some point. Those who have been informed that this often happens tend to be able to normalise their symptoms. Those who have not been informed about normal symptoms of stress may worry that they are 'over-reacting'. This is likely to add to their distress and to maintain and intensify the symptoms [11].

Aid workers have a greater tendency to deny stress-related symptoms than other people in helping professions [13]. Some believe that they have been 'trained to be tough and not to let certain feelings affect them' [143]. Teaching them the benefits of gaining relief through sharing concerns may help them to cope better in the long run.

Perhaps a parallel can be drawn with marriage preparation. If a couple have been helped to prepare, they are more likely to perceive difficulties as a normal part of married life, and to cope with them and remain together. Likewise, expatriates are likely to face difficulties at times. If they have received adequate preparation, they are more likely to be able to cope with the problems and resolve them. A lack of preparation may result in them giving up, or else developing stress-related symptoms.

As part of stress management training, expatriates should be given information about the importance of taking sufficient time to rest and relax. Excessive working hours contribute to the difficulties that can cause premature return [22]. Couples and families benefit from scheduling sufficient quality time together. Discussing how to create and maintain a strong social support network can also take place at the preparation stage.

Some organisations have found it beneficial to provide training in 'team building', and to teach expatriates about personality differences, in order to help team members to understand each other better. Acquiring an understanding of differences can be extended to understanding cross-cultural differences. The preparation package should include ample opportunity to learn about the relevant culture, so that unrealistic expectations can be exchanged for realistic ones. Unmet expectations are a common cause of frustration, and modifying them in advance can reduce difficulties later. Crisis management training will be discussed below, but it is important that training does not focus on crises to the exclusion of other potential stressors. Many expatriates cope well with political instability and war situations because the conflict is external and not aimed at them personally. Personal criticism and relationship conflict can be more detrimental [11]. Ongoing frustrations may be more harmful psychologically than short-lived traumatic events, as they can be a cause of chronic stress. Training in problem-solving skills, negotiation techniques and conflict resolution can help to reduce stress.

Many expatriates report feeling underprepared for their assignment [144], which adds to their levels of stress and uncertainty. A comprehensive preparation programme, including the components described above, could help to reduce both emotional problems and attrition among expatriates. For further information about preparation and training, see Lovell-Hawker [145] and Ehrenreich [146].

Safety while abroad

Training in crisis management may also be appropriate [147]. Many expatriates are at increased risk of experiencing traumatic incidents, perhaps related to terrorist attacks, war situations, evacuations, hostage taking, rape, robbery, riots, traffic accidents, land mines, natural disasters or illness epidemics. A crisis management package should include a security briefing covering measures to prevent crises wherever possible, by being alert to potential danger and taking precautions to enhance safety. The package should also provide information about established policies. Training can also be given in the importance of not abandoning hope during a crisis, but rather trying to engage in active problem solving, as this is associated with a reduction in negative psychological after effects [148].

In some areas, expatriates are targeted for hostage taking or assassination [149, 150]. Expatriates who are involved with humanitarian work in conflict zones may face particularly severe difficulties. Helping people on one side can be perceived as being an enemy of the other side. People suspected of war crimes may attempt to kill expatriates, fearing that they might speak out at criminal tribunals. Some expatriates are targeted because of their assumed nationality or religion, while others become targets because they have access to money or equipment (e.g. vehicles and VHS radios). It has been reported that kidnapping of aid workers has increased by 350% over the 3 years up to 2009 [151]. Although the survival rates among expatriates taken hostage mirrors that of the general population, fatalities are not rare. In 2008, at least 260 humanitarian aid workers were documented as killed, kidnapped or very seriously injured in violent attacks, representing a 12-year high. More than 60% of these incidents occurred in Sudan, Afghanistan or Somalia [151].

Kidnapping often follows cycles of terrorism, at times involving multiple victims. Unlike random crimes, kidnapping usually involves preselected targets. Crisis management

and contingency preparation seminars are now available (e.g. see www.redr.org). It is prudent for those orientating and caring for expatriates to become familiar with risk management principles.

Caring for expatriates in international settings

Sieveking *et al.* [152] remind us that, 'Regardless of how valid our selection is, and how thorough our orientation, most any employee will encounter difficulties . . . we can never leave even the best employee alone.'

As part of the preparation package, expatriates should receive information about where they can go for help should they have health problems or other difficulties overseas. Sending agencies should have a policy on this issue. For mild difficulties, information may be sufficient. In more severe cases, consultation with a health professional should be arranged. Ideally, organisations should obtain information about health services in the area, and how they can be accessed, before the expatriate arrives.

Ongoing contact from the sending agency can reduce the sense of isolation and anxiety, including anxiety about what will happen when they return home. Aycan [153] reported that, 'expatriates who feel confident about company support are likely to adjust better than those who experience uncertainty and stress about their future'. It can be useful to check that they are not working excessively long hours, and that they are taking days off regularly. They should be informed about how they can provide feedback, make requests or ask for help (practical or emotional) at any time should they require it. Adequate supervision should be provided. Inviting their suggestions for changes and improvements can foster job satisfaction. Chronic stress problems are less likely to materialise in an environment where people feel free to acknowledge difficulties and request help at an early stage.

Very little has been written about models of care that can be provided in international settings and there are no data in the literature that would distinguish one model of care as being more effective than another. The possibilities include the following.

1 Self-reliant staff who develop their own network and healthcare providers.

2 Help from national professionals (if necessary, those who are familiar with the culture of the expatriate).

3 International clinics.

4 Clinics staffed by members of the same organisation.

5 Reliance on networks that have been established by the embassy for their personnel. Telemedicine and internet advice may also be available (see next section).

Although 'self-care' is necessary (and some expatriates rely on self-diagnosis test kits and self-treatment, including self-help books for a variety of problems), it appears that most expatriates seek help from healthcare professionals for more complex medical problems. Professional help should certainly be sought in cases of psychosis, severe depression, suicidal ideation, anorexia nervosa, PTSD, serious difficulties with a child (including the possibility of abuse) or any other serious physical or mental health problem, especially if it appears to be getting worse. Organisations could increase the potential for more effective care by fostering a culture that promotes help-seeking behaviour [38].

Future trends

Expatriates can feel isolated and undervalued if they are not asked periodically how their workload is, and how they are coping personally. Satellite telephones and email links will often provide timely counsel for persons in remote regions. Self-care is often strengthened by access to reputable websites, many of which have been developed for travellers who do not have formal medical training. Patients now have the potential to access their medical records via the internet. Although care through electronic mediums is often limited to general advice rather than formulation of a specific diagnosis and management plan, one can often provide guidance that will help expatriates to determine an appropriate course of action. Results of laboratory testing can be faxed, and good-quality films from a variety of diagnostic imaging services can be couriered to a tertiary care centre for a fraction of the cost of repatriation.

Soon that will seem archaic. With technology that is currently available, telemedicine is experiencing a resurgence of interest. Several models of medical care have been developed that can serve as practical examples, such as the Yale Telemedicine Center, which has created links with physicians in Saudi Arabia. When utilising telemedicine, it is difficult to know the limits of medical licensure and difficult to determine medical-legal boundaries. Many are critical of endorsement without careful attention being given to the standards of care and the appraisal process. While caution is needed, there have been some promising outcomes for treatment by video conference ('telepsychiatry') [154], as well as internet cognitive behavioural therapy for conditions such as depression [155].

Some practitioners are exploring and starting to implement the practice of the 'client journey'. This is a patient management system or 'health pastoring', which the travellers bids into, in which the healthcare provider advises and sets up an agreed follow-up system for tracking the health and psychosocial wellbeing of the traveller from when they

first 'sign on' with an agency until they have completed their assignment.

What to do if difficulties develop while overseas

If appropriate treatment is not available locally, or the expatriate is unwilling to accept it, there may be a need for repatriation. A local medical professional may be able to liaise with the organisation in such cases. The expatriate should be helped to accept that repatriation is not a sign of failure. Comprehensive travel insurance includes cover for emergency repatriation (Medivac). By accessing the company's helpline (given on the insurance documents), travel arrangements will be made by the assistance company.

A common situation is evacuation due to deterioration in the security situation. It is very helpful if organisations have clear evacuation policies, which expatriates are asked to adhere to as a condition of their contract. It is not uncommon for expatriates to refuse to follow an evacuation policy, perhaps because they do not believe that there is any danger, or because in the heat of a crisis they develop a 'martyr instinct' and insist that they will not abandon their local friends. Expatriates who have consented to a policy before going overseas, having been informed of the reasons for it, are more likely to adhere to it later. Organisations should also have policies on such issues as abuse and hostage situations.

If an expatriate does experience evacuation or any other traumatic incident, it may be appropriate to offer psychological first aid, and possibly critical incident stress debriefing (CISD) [156]. If there are several expatriates working in close proximity, it may be beneficial to ensure that at least one of them is trained in providing psychological first aid.

CISD was originally proposed as an intervention where groups of people who had experienced a traumatic incident in the course of their work would meet together 24–72 hours after the incident, and describe in a structured way the facts about what had happened, and then their thoughts, followed by their feelings. Participants would then be helped to normalise their reactions, and then to move towards future planning.

There is considerable debate about the effectiveness of CISD. Rose *et al.* [157] identified 15 randomised controlled trials (RCTs) of CISD with individuals following unexpected traumatic events. Overall, CISD was found to have no effect, and the authors advised against its use. However, the reviewers acknowledged that the studies were of poor quality. See Lovell-Hawker [158] for a review of the evidence.

The RCTs reviewed by Rose *et al.* [157] did not involve aid workers or expatriates; more relevant research suggests CISD may be beneficial for this group. The use of CISD has been found to be associated with a significant reduction of alcohol misuse amongs soldiers returning from peace-keeping operations [159, 160]. Another RCT found that debriefing was minimally associated with lower reports of post-traumatic symptoms for peace keepers exposed to high levels of mission stress [161]. Research using matched samples indicates that debriefing appears to reduce the risk of symptoms of traumatic stress among aid workers [158]. Further research will hopefully add further insight to this debate. In the meantime, watchful waiting is recommended to see if any problems develop, so that a swift response may be offered if they do.

After any traumatic incident, it is wise to ensure that there is adequate time to rest. Accidents are more common following a stressful experience, and so the individual should be encouraged to take particular care, especially when driving. PTSD can develop months or even years after a traumatic event, perhaps being triggered by a subsequent event, and so follow-up support should be offered if the expatriate wants to receive it at any point.

Health screening and care on return

The context

Expatriates will generally be exposed to similar pathogens as other travellers. Of course they may be exposed to more of them and they may be exposed over a longer period of time.

Longer-term expatriates will have often developed different ways of perceiving themselves, their lives and the world. They may have collected a medical worry list because of local healthcare they perceive to be inadequate. They may be suffering from cumulative stress. These factors can cause or confound their medical symptoms. As a result, some will be introspectively concerned about what is going on in their bodies (and their minds), and may have consulted a range of friends either face to face or more commonly by email.

The different mindset of longer-term expatriates means that a purely mechanistic, evidence-based approach to screening is, on its own, woefully inadequate. Many expatriates will need to unravel concerns and bid into an action plan of which they feel ownership. We must be prepared to think in either postmodern or modern paradigms with this subgroup of travellers, without losing our evidence-based, cost-effective approach as the foundation of what we advise and recommend.

Purpose of post-return screening and care

Screening will be defined for the purpose of this chapter as the process of diagnosing, treating and managing any real or

perceived problem in returning expatriates that has a significant impact on their physical health or psychosocial wellbeing. Most readers will recognise this as being radically different from more technical definitions used by epidemiologists, for example: 'The systematic application of a test or enquiry, to identify individuals at sufficient risk of a specific disorder to warrant further investigations or direct preventive action, amongst persons who have not sought medical attention on account of symptoms of that disorder' [162].

In practice, the 'tropical check-up' is a hybrid, a combination of screening and case finding in such a way that the needs of the patient are met, within the limits of an affordable system. Churchill *et al.* [163] began pointing us to a model beyond that of classical, mechanistic screening. Lankester [164] has written in more detail about this holistic approach and its special value in the long-term traveller.

Evidence for the validity of screening

This continues to generate a great deal of debate [43, 165–167]. A major problem is the definition of validity, which will be defined differently by the practitioner, epidemiologist, health economist and client.

A few papers have been written on the value of screening longer-term travellers, or indeed of the major health problems they suffer while abroad. In recent years, research carried out through Geosentinel has emerged as a tool to guide physicians into the most likely travel-related health problems that correlate with destination. One especially helpful paper is that by Freedman *et al.* [168] correlating place(s) of exposure to illness found in returning travellers.

One other point to remember is that most health problems found in travellers returning from the tropics will be non-tropical in nature. This was clearly shown in a paper by Ansart *et al.* [169], who looked at illness in 622 travellers returning from the tropics.

One challenge to the accurate monitoring of illness overseas is the difficulty of travellers in accurately recalling the details of illness or threats to health that may have occurred many months previously. The most reliable way to investigate such health problems is to provide regular and systematic monitoring of expatriates' health while they are overseas. Failing that, structured questionnaires that can be reviewed prior to the clinic visit will often prompt recall of health events that might otherwise be overlooked by both the practitioner and by the expatriate who is often overwhelmed by challenges faced at the time of re-entry. Without the bedrock knowledge of what illnesses have occurred abroad, health screening on return gives only a patchy idea of the expatriates' overall state of health during their overseas posting.

The screening of the returned traveller is covered in Chapter 15. In this section we will refer only to more specific papers concerned with aid workers and expatriates.

Carroll *et al.* [170] looked at a mixed group of travellers including diplomats, long-term volunteers and trekkers. The authors concluded that screening was useful but could be largely conducted through structured history taking and relevant laboratory tests; specialist examination added little. One in four of those screened had an abnormal result. In addition, non-tropical abnormalities were found in a significant number, reflecting the value to the individual of opportunistic screening for problems unrelated to travel. Eosinophilia was found in 67 out of 852 samples, positive schistosomal antibodies in 10.7%; 18.7% had abnormalities on stool tests. Although eosinophilia is often an important marker of helminth infection, its significance should be interpreted in the context of other risk factors and the absence of eosinophilia does not rule out helminth infection [171–174].

It is important to remember that of all the helminthiases that might infect a returned expatriate, strongyloidiasis is the most important because it has the potential to cause death when dissemination occurs. This is particularly significant in an age where corticosteroid therapy and other potent immunosuppressive agents increasingly are being used for a variety of inflammatory diseases and cancer.

Peppiatt and Byass [175] looked at the health of 212 returning missionaries serving in 27 countries for 488 person-years. They found that 6.5% of adults had a raised eosinophil count, but only 13 out of 157 had cysts of pathogenic organisms on stool test, lower than in many reported studies. Self-reporting from overseas showed malaria, diarrhoea and giardia infection to be the most common perceived illnesses, but psychiatric illness accounted for nearly 110 episodes per 1,000 person-years, underlining the need for careful assessment and stress management seminars before leaving, and appropriate debriefing and counselling on return.

The screening of children returning from the tropics has been studied by Brouwer *et al.* [176] They looked at 282 check-ups of children, aged from 3 months to 16 years, with stays ranging from 3 months to 13 years. Of these, 62% were on children who had lived in sub-Saharan Africa; 156 diagnoses of travel-related infectious and parasitic illnesses were found. Quoting from figures in this paper from asymptomatic cases, 23% of check-ups showed asymptomatic giardiasis, 10% eosinophilia and 8% schistosomiasis. No consensus has been reached on the value and cost-effectiveness of screening asymptomatic children. However,

a holistic paradigm, which takes into account the broader picture of parental concern and perceived public health risks in the schools they join, probably tilts the balance in favour of screening.

Who needs a medical check-up?

In a postmodern culture, practitioners are expected to be facilitators, placing evidence and benefits before their patients and their sending agencies, so both can make informed choices; however, some will wish to consult in a more classical paradigm. Equally, there will be some employers, including the military, certain companies and many relief agencies, that will have strict pre-employment protocols that must be adhered to. Unfortunately there is often less interest in the healthcare of those who have completed their assignments.

The following outline underscores the variety of reasons for medical consultations on return from overseas.

- Significant symptoms or concerns, e.g. caused by possible malaria or dengue fever, or significant exposure to serious diseases though currently asymptomatic, e.g. Bilharzia (shistosomiasis), strongyloidiasis.
- Being fit on return but subsequently developing symptoms.
- Somatisation, with the client blaming parasites for worsening or recurrent symptoms.
- Establishing a diagnosis for an unexplained illness experienced abroad.
- Advised medical assessment and/or psychological support following high-risk assignments.
- Screening asymptomatic personnel returning from long-term assignments (often taken as longer than 6 months).

Almost any problem, worry or symptom can be presented, often representing a life crisis or chronic personal dilemma. There may be unresolved problems from overseas or from before the assignment, including a myriad of non-tropical ailments such as failed birth control, an alcoholic spouse, unexplained exhaustion, worries about debt, loss of role, temporary unemployment, a failing marriage, undisclosed rape, tormented dreams or dysfunctional team relationships.

Healthcare practitioners may well be the only person travellers have the courage to speak to about such issues. For some, quick, firm reassurance may be all that is needed; but, for others, referrals or a broader, multidisciplinary team, including ministers of religion and counsellors, will be of benefit. Some will be helped by participating in a therapy or support group, with individuals experiencing similar situations.

What should screening consist of?

History

A practitioner needs to have a wide understanding of the national guidelines for periodic health examinations, epidemiology, world geography and world news so that a practitioner can make 'informed leaps of faith' into their client's situation.

Medical history taken for expatriates needs some exploration of specific components. These include any unusual health and safety risks, psychosocial factors, failed expectations, causes of sleep disturbance, signs of abnormal stress, sexual health risks, alcohol consumption, risks specific to hostile or dangerous environments and occupational health risks from HIV, HTLV1 hepatitis B or hepatitis C. Structured, pre-filled questionnaires or protocols can provide the majority of the information and make the consultation more focused and comprehensive.

Carrying out the examination

The clinical examination seeks to substantiate the findings discovered in the history and identify signs that were not revealed by the history and investigation; this is especially important with the skin, lymph nodes, liver and spleen. Bearing in mind that most health conditions will be non-tropical in nature [169] physicians will need to be familiar with examining, giving advice or referring conditions that may affect any part of the body.

Laboratory investigations

There are two mistakes to avoid: doing too few tests, and doing too many. The minimalists risk leaving their patients dissatisfied and missing important pathology. The maximalists may do unnecessary tests out of clinical insecurity, for research interests or for medicolegal reasons. In over-testing, they risk making the tropical check-up so expensive that companies and voluntary agencies will vote with their feet and stop referring their employees [171].

In practice, we should do the minimum tests necessary consistent with evidence-based medicine, our professional judgement and the concerns of the traveller. Selective interventions are based on risk factors identified during the general assessment phase of the evaluation. There is a growing body of literature that will help the practitioner to distinguish the appropriate tests [172, 177].

With an increasing number of older travellers working abroad (for instance, after early retirement), efforts should be made to ensure that those returning from assignments

that exceed 1 year receive guideline-consistent care based on age and sex specific risk factors. When appropriate, this responsibility should be delegated to their primary care provider [42, 43].

Post-assignment HIV screening

Questions surrounding HIV testing on return are somewhat different. Aid workers may qualify for screening because of occupational and sometimes lifestyle risk. Many returning aid workers and expatriates are worried about risks, even if they are negligible. Sensitive pre-test counselling is a prerequisite to testing, and a strategy for follow-up counselling for persons found to be seropositive is essential.

Screening for other sexually transmitted infections

This has long been a neglected topic in travel medicine, and large numbers of infections almost certainly continue to be missed in aid workers and long-term expatriates, many of whom have successive sexual partners. Chlamydia is frequently asymptomatic but comparatively easy to screen for. Travel practitioners must always enquire diligently about any risk, learn to recognise denial, and either arrange appropriate tests themselves or recommend attendance at a genitourinary medicine clinic. Ward and Plourde [178] have reviewed this topic in detail.

Tuberculosis surveillance

An equally important issue is to monitor travellers who are exposed to tuberculosis to detect whether they have been infected before any signs of active infection develop. Standard screening involves TST with purified protein derivative (PPD) before and after possible exposure to tuberculosis. In North America, the Mantoux skin test with 5 tuberculin units of PPD administered intradermally is the standard protocol. Tuberculin skin testing has practical drawbacks. Many aid workers are on short-term contracts, and return to their home countries every 3, 6 or 12 months. Noncompliance with preventative health measures is common, and some are on relief registers that necessitates a rapid response when called. Arranging routine pre- and post-assignment tuberculin skin testing is difficult and is likely to have low compliance.

The positive predictive value of the TST is lower when testing persons returning from the tropics, where exposure to non-tuberculous mycobacterium (NTM) in soil and water is more common. Furthermore, when the BCG vaccination was received at the age of 6 years or older, up to 40% will have persistent positive reactions and can be an important cause of false-positive TST reactions, particularly in populations whose expected prevalence of latent TB infection is less than 10% [123].

Recently, quantiferon tests, utilising gamma interferon production from patient lymphocytes/monocytes in response to tuberculin antigen, have become increasingly popular because a single blood will obviate the need for the second visit and has a greater degree of specificity for persons who have had a BCG or exposure to NTM [179].

However, the TST is still more universally available, is highly sensitive and is still practical for persons on longer assignments and with more time to prepare.

Whether or not any pre-symptom screening is arranged, all returning travellers with a persistent cough, e.g. 3 weeks or more, especially if associated with other significant symptoms such as haemoptysis, chest pain, fever or weight loss will need careful assessment, including as a minimum a chest X-ray. Bear in mind that the sensitivity of a chest X-ray is only 70 to 80% and the specificity is in the order of 60 to 70%; therefore, when there is clinical evidence of infection, early morning sputum test, carefully collected, is recommended [123].

Concluding the consultation

At the end of the consultation, make sure that the patient does not leave in a confused muddle, especially as many issues may have been touched on and plans suggested. Furthermore, the mobile nature of this community can make follow-up communication a logistical nightmare. From the traveller's viewpoint having certainty in this area and knowing that there is an action plan, can be especially valuable when so much of life on return home is characterised by uncertainty. Patients will need to be clear about the following.

- How and when results will be relayed to them.
- How to determine the results of confidential testing, such as for HIV.
- Details of any referrals to other practitioners or specialists.
- How and whether clinical details and results will be sent through to their normal physician or family doctor.
- Whether any counselling or psychological support is agreed to and if so how this is accessed.
- Action to be taken if symptoms suggestive of malaria arise over the coming weeks.
- Follow up after any 'test of treatment or test of time' for symptoms for which no obvious cause has been found.

These concepts are currently entering orthodox medical practice and if cautiously followed are valuable tools in the follow-up of common symptoms in returning travellers [180, 181].

Reporting

A report summarising health problems noted in the history and examination, copies of all investigations and details regarding action plans may be necessary for many expatriates, especially those returning to an international assignment. If a report is to be sent to the agency, the practitioner should determine the purpose of the report, the detail required and who will be the recipient of any confidential information. Larger organisations may have a medical adviser and thus more explicit medical detail may be expected. Many organisations will have limited medical expertise among their headquarters staff and thus will only need to receive a post-assignment health clearance, or be informed of necessary detail to inform any actions needed to be taken by personnel advisers or human resources teams of their employing organisation. In both cases permission for release of information is mandatory.

Re-entry issues

For some expatriates, the most disturbing part of their experience comes when they return to their home country. Some expatriates suppress their emotions while they are overseas, in order to cope, and on return home experience extreme emotional reactions, as they begin to confront their feelings [182].

Macnair [15] found that 75% of 200 returned aid workers reported difficulty readjusting on their return. The main difficulties reported were feelings of disorientation (33%), problems getting a job (24%), lack of understanding from family and friends (17%), and financial difficulties (15%). McConnan [183] found that 73% of aid workers felt inadequately debriefed and supported on their return to the sending country. Many were not informed about sources of help available or encouraged to make use of these.

In another study [11], 60% of returned aid workers reported feeling predominantly negative emotions on their return home. The most common experiences were feeling disorientated and confused, and feeling devastated and bereaved, having left friends overseas. Some described their experience vividly, for example:

> The feeling of hollowness and absolutely 'gutted-loss' when returning to the UK just doesn't bear thinking about. Quite literally the worst experiences of my life were leaving India.
>
> For some of us this is not a homecoming but the beginning of exile. We become displaced persons (p. 25).

Expatriates and their families should be helped to prepare for their return home several months before they actually return. Preparation should include information about 'reverse culture shock'. A book such as *The art of coming home* [184] may be helpful. Assistance with practical and employment concerns is also greatly appreciated.

Debriefing: a reflective pause

It is good practice to offer personal debriefing routinely to all expatriates when they return to their home country, preferably between 1 and 3 weeks after their return. Offering debriefing routinely rather than on request is preferable, as many people do not feel that they will benefit from it until after they have received it. Moreover, some people are concerned that requesting debriefing might be taken as a sign of weakness and affect future employment prospects.

While operational debriefing focuses on tasks, personal debriefing is concerned with how expatriates have been affected personally. A structured approach can be used, along the lines of the CISD model, modified for use with an individual after multiple stressors [158, 185–187]. Debriefing should not be rushed; it generally takes at least 2 hours. The expatriate should be invited to reflect on the whole experience, paying particular attention to any traumatic incidents or longer-term stressors. Each incident or stressor can be explored. The expatriate should be asked about the worst part of the experience, but they do not need to describe this in graphic detail. They should also be asked what the best parts of the experience were, and what has been learned, to help integrate the experience as a whole and find meaning in it. There should be an opportunity to discuss how the expatriate feels about being back 'home', and for the debriefer to provide information about the readjustment process.

Personal debriefing should help the expatriate to normalise any symptoms of stress, and move on towards thinking about the future. Information should be given about sources of further help should this be desired, and a follow-up contact should be arranged. Debriefing along these lines can also be offered to groups [47]. The process can be used with families, and it is certainly important to include older teenagers.

Approximately 25% of returned aid workers report clinically significant symptoms of avoidance and intrusive thoughts months after returning from a post overseas [188]. Although they do not necessarily meet the diagnostic criteria for PTSD, such symptoms are distressing and can interfere with normal functioning. One study indicated that after a single session of personal debriefing, lasting on average about 2 hours, only 7% of aid workers reported clinically significant levels of avoidance or intrusion [188]. This suggests that personal debriefing may play an

important role in preventing the development of PTSD-related symptoms.

Debriefing may also help to prevent depression. Approximately 36% of aid workers report developing depression shortly after their return home [11]. In many cases this is related to difficulty readjusting to life at home, or to a sense of meaninglessness. A skilled debriefer can guide the expatriate towards identifying a sense of meaning in the overseas experience, and help to normalise the adjustment process. People who have received debriefing may also be more likely to accept further help, such as counselling, if this is required.

Expatriates generally feel very tired when they return home, and benefit from ample time to rest before resuming work. For longer-term expatriates, it might take months to fully adjust [11]. Care should be taken to support them through this transition period, and not put pressure on them to prepare quickly for another overseas assignment.

Conclusions

The vast majority of expatriates enjoy their time overseas, despite the inevitable difficulties that they meet along the way. To help maximise both their productivity and their satisfaction, it is useful to follow certain guidelines. First, selection methods should be chosen carefully, and should include a medical review and a psychological assessment interview. Such assessments can help in placing expatriates appropriately and can serve to enhance care by ensuring that the agency assumes appropriate responsibility for the needs of their personnel.

Second, training should prepare personnel to recognise common medical problems, apprise them of the appropriate preventive strategies, and equip them to recognise signs of illness and how to deal with emergencies. There should also be teaching that covers techniques of stress management, problem solving, safety, crisis management and coping strategies aimed at helping expatriates acknowledge, normalise and request help for any stress-related problems that may develop. Comprehensive medical insurance must be in place.

While overseas, the expatriate should continue to receive support, and procedures should be in place for ensuring that help is available should problems develop. The expatriate should be offered help in preparing for the return home. Psychological support after return should be routine and an opportunity should be provided for an independent medical assessment, with further support as necessary. Sufficient time should be provided for rest and readjustment. If a partner or family is involved, support should also be available for them.

Finally, there is a need for further research in this area, appraising critically the value of screening, the impact of prevention strategies, the effects of training, the efficacy and extent to which one can become meaningfully involved with telecommunication, the role and value of health assessments on return and further evaluation of the effects of different forms of debriefing and psychological support among different types of expatriate groups. This will help to ensure that care-givers, while being cost-sensitive, do all that they can to help take care of expatriates' psychological and physical health during each stage of the journey.

Note

Some of the comments in this chapter by InterHealth linked authors do not necessarily reflect the opinions of the organisation.

References

1. People In Aid (2004) *Human Resources Manual*. People In Aid, London.
2. OECD (2009) Database on Immigrants and Expatriates (Document on the Internet). Organisation for Economic Co-operation and Development (updated 2005 Nov), http://www.oecd.org/document/51/0,3343,en_2649_ 33931_ 34063091_1_1_1_1,00.html (accessed 9 November 2009).
3. Greenwood BM (1991) Malaria chemoprophylaxis in endemic regions. In: Targett GA (ed.) *Malaria: Waiting for the Vaccine*, pp. 83–104. London School of Hygiene and Tropical Medicine, Chichester.
4. Price GB (1913) Discussion on the cause of invaliding from the troops. *Br Med J* **2**: 1290–1296.
5. Gordon LV (1967) Clinical, psychometric, and work-sample approaches in the prediction of success in Peace Corps training. *J Appl Psychol* **51**: 111–119.
6. Lange WR *et al.* (1994) Psychological concerns of overseas employees and families. *Travel Med Int* **12**: 176–181.
7. Karson S and O'Dell JW (1987) Personality profiles in the US foreign service. In: Butcher JN and Speelberger CD (eds) *Advances in Personality Assessment*, pp. 1–12. Laurence Earlbaum, Hillsdale, NJ.
8. Bernard KW *et al.* (1989) Epidemiological surveillance in Peace Corps volunteers: a model for monitoring health in temporary residents of developing countries. *Int J Epidemiol* **18**: 220–226.
9. Lange WR *et al.* (1994) Morbidity among refugee relief workers. *J Travel Med* **1**: 111–112.
10. Dahlgren A *et al.* (2009) Health risks and risk-taking behaviors among International Committee of the Red Cross (ICRC) expatriates returning from humanitarian missions. *J Travel Med* **16**(6): 382–390.
11. Lovell DM (1997) Psychological adjustment among returned overseas aid workers. DClinPsy (thesis). University of Wales, Bangor.

12. ICRC (1994) *Humanitarian Action in Conflict Zones: Coping with Stress, ICRC Guidelines*. Comrex, Geneva, p. 10.
13. Chester RM (1983) Stress on missionary families living in 'other culture' situations. *J Psychol Christianity* **2**: 30–37.
14. Richardson J (1992) Psychopathology in missionary personnel. In: O'Donnell KS and O'Donnell ML (eds) *Missionary Care*, pp. 89–109. William Carey Library, Pasadena, CA.
15. Macnair R (1995) *Room for Improvement: The Management and Support of Relief and Development Workers*. Overseas Development Institute, London.
16. Dye SF (1974) Decreasing fatigue and illness in field-work. *Missiology* **2**: 79–109.
17. Austin CN and Beyer J (1984) Missionary repatriation: an introduction to the literature. *Int Bull Missionary Res* **4**: 68–70.
18. Foyle MF (2001) *Honourably Wounded*. Monarch Books, London.
19. Parshall P (1988) How spiritual are missionaries? In: O'Donnell K.S. and O'Donnell ML (eds) *Helping Missionaries Grow: Readings in Mental Health and Missions*, pp. 75–82. William Carey Library, Pasadena, CA.
20. Donovan K (1992) *The Pastoral Care of Missionaries*. Commodore Press, Lilydale.
21. Carr K (1994) Trauma and post-traumatic stress disorder among missionaries. *Evangelical Missions Quarterly* **30**: 246–253.
22. Lovell DM (1999) Chronic fatigue syndrome among overseas development workers: a qualitative study. *J Travel Med* **6**: 16–23.
23. Paton D and Purvis C (1995) Nursing in the aftermath of disaster: orphanage relief work in Romania. *Disaster Prevention and Management* **4**: 45–54.
24. Goldberg DP *et al*. (1976) A comparison of two psychiatric screening tests. *Br J Psych* **129**: 61–67.
25. Horowitz MJ *et al*. (1979) Impact of event scales: a measure of subjective distress. *Psychosomatic Med* **41**: 209–218.
26. Paton D (1992) International disasters: issues in the management and preparation of relief workers. *Disaster Management* **4**: 183–190.
27. Lopes Cardozo B and Salama P (2002) Mental health of humanitarian aid workers in complex emergencies. In: Danieli Y (ed.) *Sharing the Front Lines and the Back Hills*, pp. 242–255. Baywood Publishers, New York.
28. Mollica RF *et al*. (2004) Mental health in complex emergencies. *Lancet* **364**: 2058–2067.
29. Brierley PW (1997) Missionary attrition: the ReMAP research report. In: Taylor WD (ed.) *Too Valuable to Lose*, pp. 85–102. William Carey Library, Pasadena, CA.
30. Deshpande SP and Viswesvaran C (1992) Is cross-cultural training of expatriate managers effective: a meta analysis. *Int J Intercultural Relations* **16**: 295–310.
31. Harzing AK (1995) The persistent myth of high expatriate failure rates. *Int J Hum Resource Manage* **6**: 457–473.
32. Tung RL (1988) *The New Expatriates: Managing Human Resources Abroad*, Ballinger. Cambridge, MA.
33. Schouten EJ and Borgdorff MW (1995) Increased mortality among Dutch development workers. *Br Med J* **311**: 1343–1344.
34. Frame JD *et al*. (1992) Mortality trends of American missionaries in Africa, 1945–1985. *Am Soc Trop Med Hyg* **46**: 686–690.
35. Hargarten SW and Baker SP (1985) Fatalities in the Peace Corps. A retrospective study: 1962 through 1983. *JAMA: J Am Med Assoc* **254**: 1326–1329.
36. Peytremann I *et al*. (2001) Medical evacuations and fatalities of United Nations high commissioner for refugees field employees. *J Travel Med* **8**(3): 117–121.
37. People In Aid (2003) *Code of Good Practice in the Management and Support of Aid Personnel*. People In Aid, London.
38. MMWR (1999) Ten Great Public Health Achievements (Document on the Internet). MMWR, United States of America (updated 2001 May 2), http://www.cdc.gov/mmwr/preview/mmwrhtml/00056796.htm (accessed 29 November 2009).
39. Boulware LE *et al*. (2007) Systematic review: the value of the periodic health evaluation. *Ann Int Med* **146**(4): 289–300.
40. Smolinski M (2000) *Healthy People 2010: Understanding and Improving Health*. Washington: U.S. Department of Health and Human Services.
41. Ruffin MT *et al*. (2000) Predictors of screening for breast, cervical, colorectal, and prostatic cancer among community-based primary care practices. *J Am Board Fam Pract/Am Board Fam Pract* **13**(1): 1–10.
42. Atlas SJ *et al*. (2009) Patient-physician connectedness and quality of primary care. *Ann Int Med* **150**(5): 325–335.
43. Bindman A (2009) Is there a personal doctor in the house? *Ann Intern Med* **150**: 351–352.
44. Hayward SA *et al*. (1991) Preventive care guidelines: 1991. *Ann Int Med* **114**: 758–783.
45. Paluszny M and Zrull JP (1971) The new missionary: a review of 50 candidates. *Arch Gen Psychiat* **24**: 363–366.
46. McCall M and Salama P (1999) Selection, training and support of relief workers: an occupational health issue. *Br Med J* **318**: 113–116.
47. Fawcett G (1999) *Ad-Mission: The Briefing and Debriefing of Teams of Missionaries and Aid Workers*. Self-published: Harpenden, England.
48. Oates D (1970) What it takes to work abroad. *Int Manage* **10**: 24–27.
49. Holmes WF and Piker FK (1980) Expatriate failure-prevention rather than cure. *Pers Manage* **12**: 30–32.
50. Hathaway SR and McKinley JC (1989) *Minnesota Multiphasic Personality Inventory-2*. University of Minnesota Press, Minneapolis.
51. Westefeld JS and Maples M (1998) The MMPI-2 and vocational assessment: a brief report. *J Career Assess* **6**: 107–113.
52. Schubert E (1992) Current issues in screening and selection. In: O'Donnell K and O'Donnell ML (eds) *Missionary Care*, pp. 74–88. William Carey Library, Pasadena, CA.
53. Butcher JN (1996) *International Adaptations of the MMPI-2*. University of Minnesota Press, Minneapolis.
54. Guthrie GM and Zektick IN (1967) Predicting performance in the Peace Corps. *J Soc Psychol* **71**: 11–21.
55. Dicken C (1969) Predicting the success of peace corps community development workers. *J Consult Clin Psychol* **33**: 597–606.
56. Dillon DE (1983) Personality characteristics of evangelical missionaries as measured by the MMPI. *J Psychol Theol* **11**: 213–217.

57. Schnurr PP *et al.* (1993) Premilitary MMPI scores as predictors of combat-related PTSD symptoms. *Am J Psychiat* **150**: 479–483.
58. Schubert E and Ganter K (1996) The MMPI as a predictive tool for missionary candidates. *J Psychol Theol* **24**: 124–132.
59. Schubert E (1999) A suggested prefield process for missionary candidates. *J Psychol Theol* **27**: 87–97.
60. Hargrave GE *et al.* (1994) Comparison of the MMPI and the MMPI-2 for a sample of peace offers. *Psychol Assess* **6**: 27–32.
61. Doll RE *et al.* (1969) Relative predictability of occupational groups and performance criteria in an extreme environment. *J Clin Psychol* **25**: 399–402.
62. Ones DZ and Viswesvaran C (1997) Personality determinants in the prediction of aspects of expatriate job success. In: Aycan Z (ed.) *New Approaches to Employment Management, Expatriate Management: Theory and Research* 4, pp. 63–92. Jai Press, Greenwich, CT.
63. Piedmont R *et al.* (2000) On the invalidity of validity scales. *J Pers Soc Psychol* **78**: 582–593.
64. Rosse J *et al.* (1998) The impact of response distortion on preemployment personality testing and hiring decisions. *J Appl Psychol* **83**: 634–644.
65. Birkeland S *et al.* (2006) A meta-analytic investigation of job applicant faking on personality measures. *Int J Selec Assess* **14**: 317–335.
66. Hirsh JB and Peterson JB (2008) Predicting creativity and academic success with a 'fake-proof' measure of the Big Five. *J Res Pers* **42**: 1323–1333.
67. Ryan A *et al.* (1999) An international look at selection practices. *Pers Psychol* **52**: 359–362.
68. Carter J (1999) Missionary stressors and implications for care. *J Psychol Theol* **27**: 171–180.
69. Foyle MF *et al.* (1998) Expatriate mental health. *Acta Psychiat Scand* **97**: 278–283.
70. Stroh LK *et al.* (1994) Predictors of expatriate adjustment. *Int J Org Anal* **2**: 176–192.
71. Sweatman SM (1999) Marital satisfaction, cross-cultural adjustment stress, and the psychological sequelae. *J Psychol Theol* **27**: 154–162.
72. Foyle MF (1994) Expatriate children: selection, preparation, and typical needs. *Travel Med Int* **12**: 93–97.
73. Fisher J *et al.* (1967) Validity of the psychiatric interview. Predicting the effectiveness of the first Peace Corps volunteers in Ghana. *Arch Gen Psychiat* **17**: 744–750.
74. Gunderson EK and Kapfer EL (1966) The predictive validity of clinical ratings for an extreme environment. *Br J Psychiat* **112**: 405–412.
75. Callahan MV and Hamer DH (2005) On the medical edge: preparation of expatriates, refugee and disaster relief workers, and Peace Corps volunteers. *Infect Dis Clin N Am* **19**(1): 85–101.
76. Hutin YJF *et al.* (2003) Use of injections in healthcare settings worldwide, 2000: literature review and regional estimates. *Br Med J* **327**: 1075–1080.
77. Lange WR and Frame JD (1990) High incidence of viral hepatitis among American missionaries in Africa. *Am J Trop Med Hyg* **43**: 527–533.
78. Smalligan RD *et al.* (1995) The risk of viral hepatitis A, B, C, and E among North American missionaries. *Am J Trop Med Hyg* **3**: 233–236.
79. Vaughn D and Hoke C (1992) The epidemiology of Japanese encephalitis: prospects for prevention. *Epidemiol Rev* **14**: 197–221.
80. Centers for Disease Control and Prevention (1993) Inactivated Japanese encephalitis virus vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR: Morbid Mortal Wkly Rep* **42**(1111–1): 1–15.
81. Cieslak P (2009) ACIP Meeting June 2009 (Document on the Internet). ACIP JEV vaccines workgroup, http://www.cdc.gov/vaccines/recs/acip/downloads/mtg-slides-jun09/08-je.pdf (accessed 28 November 2009).
82. Arguin PM *et al.* (2000) Survey of rabies preexposure and postexposure prophylaxis among missionary personnel stationed outside the United States. *J Travel Med* **7**: 10–14.
83. Bernard KW and Fishbein DB (1991) Pre-exposure rabies prophylaxis for travellers: are the benefits worth the cost? *Vaccine* **9**: 833–836.
84. Bjorvatn B and Gundersen SG (1980) Rabies exposure among Norwegian missionaries working abroad. *Scand J Infect Dis* **12**: 257–264.
85. Hatz CF *et al.* (1994) Circumstances and management of 72 animal bites among long-term residents in the tropics. *Vaccine* **13**: 811–815.
86. LeGuerrier P *et al.* (1996) Pre-exposure rabies prophylaxis for the international traveller: a decision analysis. *Vaccine* **14**: 167–176.
87. ACIP (2009) Provisional Recommendations: Prevention of Human Rabies (document on the Internet). National Center for Immunization and Respiratory Diseases, 2009 (updated 2009 Oct 20), http://www.cdc.gov/vaccines/recs/provisional/downloads/rabies-July2009-508.pdf (accessed 28 November 2009).
88. MMWR (2008) Human rabies prevention – United States. *Recommendations of the Advisory Committee on Immunization Practices* **1–26**: 28.
89. World Health Organization (2004) *Cholera Vaccines: A New Public Health Tool?* WHO, Geneva.
90. Dijkstra JA *et al.* (2005) Vaccine-preventable diseases in long-term expatriates. *J Travel Med* **12**: S47–S57.
91. Adera T *et al.* (1995) Risk factors for malaria among expatriates living in Kampala, Uganda: the need for adherence to chemoprophylactic regimens. *Am J Trop Med* **52**: 207–212.
92. Ohrt C *et al.* (1997) Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. *Ann Intern Med* **126**: 963–672.
93. Schneider G (1998) Malaria prevention for long-term workers overseas. Choice or necessary evil? MSc (thesis). University of London.
94. Peppiatt R and Byass P (1990) Risk factors for malaria among British missionaries living in tropical countries. *J Trop Med Hyg* **93**: 397–402.
95. Phillips-Howard P *et al.* (1990) Risk of malaria in British residents returning from malarious areas. *Br Med J* **300**: 499–503.
96. Lobel HO *et al.* (1998) Monitoring for mefloquine-resistant Plasmodium falciparum in Africa: implications for travellers' health. *Am J Trop Med Hyg* **59**: 129–132.

97. Keystone JS (2004) The sound of hoof beats does not always mean that it is a zebra. *Clin Infect Dis* **39**(11): 1589–1590.
98. Eono P *et al*. (1999) Malaria in expatriates in Abidjan. *Medecine Tropicale: Revue du Corps de Sante Colonial* **59**: 358–364.
99. Carme B (1993) Antimalarial measures in expatriates in the Congo: trends 1989–1992. *Ann Soc Belge Med Trop* **73**: 91–99.
100. Toovey S *et al*. (2007) Special infectious disease risks of expatriates and long-term travelers in tropical countries. *Part I: Malaria*. *J Travel Med* **14**(1): 42–49.
101. Chen LH *et al*. (2006) Prevention of malaria in long-term travelers. *JAMA: J Am Med Assoc* **296**(18): 2234–2244.
102. Lobel HO *et al*. (1991) Effectiveness and tolerance of long-term malaria prophylaxis with mefloquine. Need for a better dosing regimen. *JAMA: J Am Med Assoc* **265**: 361–364.
103. Lobel HO *et al*. (1993) Long-term malaria prophylaxis with weekly mefloquine. *Lancet* **341**: 848–851.
104. Schlagenhauf P *et al*. (1996) Mefloquine tolerability during chemoprophylaxis: focus on adverse event assessments, stereochemistry and compliance. *Trop Med Int Health* **4**: 485–494.
105. Jacquerioz FA and Croft AM (2009) Drugs for preventing malaria in travellers. *Meta-Analysis Review 2009*. Report No.: 1469-493X (Electronic) 1361-6137 (Linking) Contract No.: 4.
106. Kain KC *et al*. (2001) Malaria deaths in visitors to Canada and in Canadian travellers: a case series. *CMAJ: Can Med Assoc J* **164**: 654–659.
107. Friman G *et al*. (1983) Agranulocytosis associated with malaria prophylaxis with Maloprim. *Br Med J* **286**: 1244–1245.
108. Public Health Agency of Canada (2009) *Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers*, vol. 35S1. Public Health Agency of Canada, Canada.
109. Banchongaksorn T *et al*. (1996) A field trial of the ParaSight-F test for the diagnosis of Plasmodium falciparum infection. *Trans Roy Soc Trop Med Hyg* **90**: 244–245.
110. Pieroni P *et al*. (1998) Comparison of the ParaSight-F test and the ICT Malaria Pf test with the polymerase chain reaction for the diagnosis of Plasmodium falciparum malaria in travellers. *Trans Roy Soc Trop Med Hyg* **92**: 166–169.
111. Mills CD *et al*. (1999) Evaluation of a rapid and inexpensive dipstick assay for the diagnosis of Plasmodium falciparum malaria. *Bull World Health Organ* **77**: 553–559.
112. Funk M *et al*. (1999) MalaQuick versus ParaSight F as a diagnostic aid in travellers' malaria. *Trans Roy Soc Trop Med Hyg* **93**: 268–272.
113. Trachsler M *et al*. (1999) Feasibility of a rapid dipstick antigen-capture assay for self-testing of travellers' malaria. *Trop Med Int Health* **4**: 442–447.
114. Whitty CJM *et al*. (2000) Self-testing for falciparum malaria with antigen-capture cards by travelers with symptoms of malaria. *Am J Trop Med Hyg* **63**(5–6): 295–297.
115. Kremsner PG *et al*. (1999) Atovaquone and proguanil hydrochloride for treatment of malaria. *J Travel Med* **6**: S18–S20.
116. Nosten F and White NJ (2007) Artemisinin-based combination treatment of falciparum malaria. *Am J Trop Med Hyg* **77**: 181–192.
117. Kain KC and Keystone JS (1998) Malaria in travelers. Epidemiology, disease, and prevention. *Infect Dis Clin N Am* **12**: 267–284.
118. McGready R *et al*. (2004) Malaria and the pregnant traveler. *Travel Med Infect Dis* **2**: 127–142.
119. World Health Organization (1998) *Tuberculosis. Fact Sheet No. 104*. WHO, Geneva.
120. Cobelens FG *et al*. (2000) Risk of infection with Mycobacterium tuberculosis intravellers to areas of high tuberculosis endemicity. *Lancet* **356**: 461–465.
121. Behr MA and Small PM (1997) Has BCG attenuated to impotence? *Nature* **389**: 133–134.
122. Department of Health (2006) Immunisation Against Infectious Disease – The Green Book [updated edition], http://www.dh.gov.uk/en/Publichealth/Healthprotection/Immunisation/Greenbook/dh_4097254 (accessed 30 November 2009).
123. Long R and Ellis E (eds) (2007) *Canadian Tuberculosis Standards*, 6th edn. Minister of Health, Canada.
124. Hoge CW *et al*. (1996) Epidemiology of diarrhea among expatriate residents living in a highly endemic environment. *JAMA: J Am Med Assoc* **275**: 533–538.
125. Shlim DR *et al*. (1999) Persistent high risk of diarrhea among foreigners in Nepal during the first 2 years of residence. *Clin Infect Dis* **29**: 613–616.
126. Gaudio PA *et al*. (1996) Diarrhea among expatriate residents in Thailand: correlation between reduced campylobacter prevalence and longer duration of stay. *J Travel Med* **3**(2): 77–79.
127. De Graaf R *et al*. (1998) Occupational risk of HIV infection among western health care professionals posted in AIDS endemic areas. *AIDS Care* **4**: 441–452.
128. Hamer DH *et al*. (2008) Knowledge and use of measures to reduce health risks by corporate expatriate employees in western Ghana. *J Travel Med* **15**(4): 237–242.
129. Moore J *et al*. (1995) HIV risk behavior among peace corps volunteers. *AIDS* **9**: 795–799.
130. Bonneux L *et al*. (1988) Risk factors for infection with human immunodeficiency virus among European expatriates in Africa. *Br Med J* **297**: 581–584.
131. Rowbottom J (1993) STDs and the overseas traveller. *Aust Fam Phys* **22**: 125–131.
132. Mabey D (1995) Sex and travel. *Br J Hosp Med* **54**: 264–266.
133. De Graaf R *et al*. (1997) Sexual risk of HIV infection among expatriates posted in AIDS endemic areas. *AIDS* **11**: 1173–1181.
134. Lange WR *et al*. (1989) Are missionaries at risk for AIDS? Evaluation for HIV antibodies in 3207 protestant missionaries. *Southern Med J* **82**: 1075–1078.
135. Lange WR and Frame JD (1991) Assessment of risk for HIV-1 infection for missionaries in sub-Saharan Africa. *Southern Med J* **84**: 193–197.
136. Houweling H and Coutinho RA (1991) Risk of HIV infection among Dutch expatriates in sub-Saharan Africa. *Int J STD AIDS* **4**: 252–257.
137. World Health Organization (1999) *AIDS Not Losing Momentum. WHO Press Release No. 66*. WHO, Geneva.
138. Médicins Sans Frontières (1997) *Procedures to Be Followed after An Accidental Exposure to Blood*. MSF, Holland.
139. Christy RL and Rasmussen JE (1963) Human reliability implications of the US Navy's experience in screening and selection procedures. *Am J Psychiat* **120**: 540–547.

140. Dally P (1985) Psychiatric illness in expatriates. *J Roy Coll Phys Lond* **19**: 103–104.
141. Henry ER (1965) What business can learn from Peace Corps selection and training. *Personnel* **42**: 17–25.
142. Hay R *et al.* (2007) *Worth Keeping: Global Perspectives on Best Practice in Missionary Retention*. William Carey Library, Pasadena, CA.
143. Grant R (1995) Trauma in missionary life. *Missiology* **23**: 71–83.
144. Dunbar E and Ehrlich MH (1993) Preparation of the international employee: career and consultation needs. *Consult Psychol J* **45**: 18–24.
145. Lovell-Hawker D (2009) *Supporting Staff Responding to Disasters: Recruitment, Briefing and on-Going Care*. People In Aid, London.
146. Ehrenreich JH (2005) *The Humanitarian Companion: A Guide for International Aid, Development and Human Rights Workers*. ITDG Publishing, Rugby, England.
147. Goode GS (1995) Guidelines for crisis and contingency management. *Int J Frontier Missions* **12**: 211–216.
148. Ehlers A *et al.* (1998) Predicting response to exposure treatment in PTSD: the role of mental defeat and alienation. *J Traumatic Stress* **11**: 457–471.
149. Slim H (1995) The continuing metamorphosis of the humanitarian practitioner: some new colours for an endangered chameleon. *Disasters* **19**: 110–126.
150. Rogers C (1998) The changing shape of security for NGO field workers. *Together*, 9–11.
151. Stoddard A *et al.* (2009) *Providing Aid in Insecure Environments: 2009 Update*. Overseas Development Institute, London.
152. Sieveking N *et al.* (1981) Selecting and preparing expatriate employees. *Pers J* **60**: 197–202.
153. Aycan Z (1997) Acculturation of expatriate managers: a process model of adjustment and performance. In: Aycan Z (ed.) *New Approaches to Employee Management, Vol. 4, Expatriate Management: Theory and Research*, pp. 1–40. Jai Press, Greenwich, CT.
154. Ruskin PE *et al.* (2004) Treatment outcomes in depression: comparisons of remote treatment through telepsychiatry to in-person treatment. *Am J Psychiat* **161**: 1471–1476.
155. Titov N (2007) Status of computerized cognitive behavioural therapy for adults. *Aust NZ J Psychiat* **41**: 95–114.
156. Mitchell JT (1983) When disaster strikes. *J Emerg Med Serv* **8**: 36–39.
157. Rose S *et al.* (2006) Psychological debriefing for preventing post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev* [Review] 2002(2): CD000560.
158. Lovell-Hawker D (2009) *Debriefing Aid Workers and Missionaries: A Comprehensive Manual*. People In Aid, London.
159. Deahl MP *et al.* (2001) Evaluating psychological debriefing: are we measuring the right outcomes? *J Traumatic Stress* **14**: 527–529.
160. Deahl MP *et al.* (2000) Preventing psychological trauma in soldiers: the role of operational stress training and psychological debriefing. *Br J Med Psychol* **73**: 77–85.
161. Adler AB *et al.* (2008) A group randomized trial of critical incident stress debriefing provided to U.S. peacekeepers. *J Traumatic Stress* **21**: 253–263.
162. Department of Health (1997) *Annual Report of the National Screening Committee*. DOH, London.
163. Churchill DR *et al.* (1993) Screening the returned traveller. *Br Med Bull* **49**: 465–474.
164. Lankester TE (2005) Health care of the long-term traveller. *Travel Med Infect Dis* **3**: 143–155.
165. Conlon CP (1993) Post-tropical screening is of little value. *Br Med J* **307**: 1008.
166. Genton B and Gehri M (1999) Routine screening of children returning home from the tropics. Authors' definition of asymptomatic children is not the one usually accepted. *Br Med J* **319**: 121–122.
167. Okereke E and Gelletie R (1999) Letter. *Br Med J* **319**: 121–122.
168. Freedman D *et al.* (2006) Spectrum of disease and relation to place of exposure among ill retuned travellers. *New Engl J Med* **354**: 119–130.
169. Ansart S *et al.* (2005) Illness in travelers returning from the tropics: a prospective study of 622 patients. *J Travel Med* **12**: 312–318.
170. Carroll B *et al.* (1993) Post-tropical screening: how useful is it? *Br Med J* **307**: 541.
171. Libman MD *et al.* (1993) Screening for schistosomiasis, filariasis, and strongyloidiasis among expatriates returning from the tropics. *Clin Infect Dis* **17**: 353–359.
172. MacLean JD and Libman M (1998) Screening returning travelers. *Infect Dis Clin N Am* **12**: 431–443.
173. Moore TA and Nutman TB (1998) Eosinophilia in the returning traveler. *Infect Dis Clin N Am* **12**: 503–521.
174. Meltzer E *et al.* (2008) Eosinophilia among returning travelers: a practical approach. *Am J Trop Med Hyg* **78**(5): 702–709.
175. Peppiatt R and Byass P (1991) A survey of the health of British missionaries. *Br J Gen Pract* **41**: 159–162.
176. Brouwer ML *et al.* (1999) Routine screening of children returning home from the tropics: retrospective study. *Br Med J* **318**: 568–569.
177. MacPherson DW (1999) Intestinal parasites in returned travelers. *Med Clin N Am* **83**: 1053–1075.
178. Ward B and Plourde P (2006) Travel and sexually transmitted infections. *J Travel Med* **13**: 300–317.
179. Manuel O and Kumar D (2008) QuantiFERON-TB Gold assay for the diagnosis of latent tuberculosis infection. *Expert Rev Mol Diagn* **8**(3): 247–256.
180. Glasziou P *et al.* (2009) Diagnosis using 'test of treatment'. *Br Med J* **338**: b1312.
181. Almond S and Summerton N (2009) Diagnosis in general practice. Test of time. *Br Med J* **339**: 43–45.
182. Smith B *et al.* (1996) Health activities across traumatized populations: emotional responses of international humanitarian aid workers. In: Danieli Y *et al.* (eds) *International Responses to Traumatic Stress: Humanitarian, Human Rights, Justice, Peace and Development Contributions, Collaborative Actions and Future Initiatives*, pp. 397–422. Baywood, New York.
183. McConnan I (1992) *Recruiting Health Workers for Emergencies and Disaster Relief in Developing Countries*. International Health Exchange, London.

184. Storti C (1991) *The Art of Coming Home*. Intercultural Press, Yarmouth, ME.
185. Armstrong KR *et al*. (1995) Multiple stressor debriefing and the American Red Cross: the East Bay Hills fire experience. *Social Work* **40**: 83–90.
186. Adler AB *et al*. (2008) Time-driven Battlemind Psychological debriefing: a group level early intervention in combat. *Mil Med* **174**: 22–28.
187. Adler AB *et al*. (2009) Battlemind debriefing and battlemind training as early interventions with soldiers returning from Iraq: randomization by platoon. *J Consult Clin Psychol* **77**(5): 928–940.
188. Lovell DM (1999) *Evaluation of Tearfund's Critical Incident Debriefing Process*. Tearfund, Teddington.

Chapter 29 The health of migrants and refugees

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Introduction

While different types of traveller are characterised essentially by the purpose of their travel (tourism, business, etc.), various categories of migrants fall into different administrative and legal statuses, each with specific consequences in terms of duration of residence, access to services, rights and obligations. This is a fundamental difference that health practitioners should understand and remember when they see people who are migrants or refugees. Travellers are free to move anywhere and can have unlimited access to services, limited only by the availability of financial resources. Migrants, however, are bound by regulations and rules beyond their control. They are also likely to have experienced long and often painful administrative procedures and often are waiting for decisions that are pending and which create major uncertainties about their future. From a public health perspective they are all mobile populations and contribute to the overall impact of global mobility. They share some common factors related to travel and exposure to new environments and risks. However, migrants and travellers are very different in terms of access to health and care determined by their status, conditions of travel and living, duration of residence and overall personal experiences.

Although this chapter discusses the health issues and medical problems of migrants from a health practitioner's perspective, it is important to remember that most migrants are healthy and benefit from the 'healthy migrant effect', i.e. those moving and ready to leave their country are healthy and dynamic. Migration is not an easy decision; it tends to select the fittest rather than sick individuals. However, the conditions that may prevail in the migration process can increase vulnerability and be detrimental to health.

Trends in population movement

The International Organization for Migration (IOM) estimates that there are more than 214 million international migrants in the world today [1]. Migrants comprise 3% of the global population and they would constitute the fifth most populous country in the world. Migration movements are by no means limited to south–north migration. South–south migration (61 million) is almost equivalent to south–north migration (62 million). Increasingly, intra-regional movements are seen to take place in Asia and major internal movements are seen within emerging economies such as Brazil, India and China.

The majority of migrants, however, move within their own country (740 million people) [2] (*see* Table 29.1). From 1970 to 2000 in North America, migrant stocks increased from 15.9% to 23.3% [1]. Europe continues to attract international migrants while it develops a common immigration space. The migrant population in Europe in 2005 was estimated at 64.1 million, i.e. 8.8% of the total population, with 53.3 million in Asia and 44.5 million in North America respectively. Migrants represent 20% of the population in Switzerland, 12% in Germany, 11% in France and 10% in the UK.

By the end of 2009, there were 43.3 million forcibly displaced people worldwide. This includes 15.2 million refugees, 983,000 asylum seekers and 27.1 million internally displaced persons (IDPs) [3]. Women and girls represent on average 49% of persons of concern to the United Nations High Commissioner for Refugees (UNHCR) and they constitute 47% of refugees and asylum seekers, and half of all IDPs and returnees (refugees). Forty-one per cent of refugees and asylum seekers are children below 18 years of age. The UNHCR concludes that four out of five refugees reside in developing countries, more than three-quarters of the

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Table 29.1 Global estimates of migrant populations

Internal migrants	~ 740 million (stock in 2009)
Immigrants	Annual flow between 2005–10 ~ 2.7 million with a stock of ~ 214 million international migrants in 2010
Migrant workers	~ 100 million (stock in 2009)
International students	~ 2.1 million (stock in 2003)
Internally displaced persons	51 million (stock in 2007) includes those displaced by natural disasters and conflict (UNHCR)
Refugees	15.2 million (stock beginning of 2009)
Asylum seekers or refugee claimants	838,000 (stock beginning of 2009
Temporary – recreational or business travel	922 million in 2008
Trafficked persons (across international borders)	Estimated 800,000 per year (2006). There are no accurate estimates of the stocks and flows of people who have been trafficked

Adapted from: WHO (2010) Health of Migrants – the way forward. Report of a global consultation. Madrid, Spain, 3-5 March 2010. http://www.who.int/hac/events/consultation_report_health_migrants_colour_web.pdf.

world's refugees seek asylum in neighbouring countries or in an immediate region, and one out of two refugees lives in an urban area. A total of 922,000 claims for asylum were recorded in 2009, with Europe remaining the primary destination for individual asylum seekers, followed by Africa (South Africa), the Americas and Asia.

As the number of migrants seeking access to industrialised countries increases, tighter regulations and boarder controls have led to an increase in irregular migration and in the human trafficking of migrants. Irregular migration is estimated to affect 600,000 to 800,000 persons per year. Europe is believed to host between 7 and 8 million irregular migrants and it is estimated that there were 11 million unauthorised migrants in the United States in 2006 [4]. Trafficking has become a very lucrative illegal market with worldwide ramifications. Travel conditions may be horrendous and very risky. It is estimated that between 1988 and 2008, 1,600 persons died crossing the Sahara desert to North Africa and 8,173 were drowned crossing the Mediterranean Sea [5].

There are new factors contributing to the movement of people worldwide, including the rapid urbanisation of developing countries, particularly in Africa and Asia. Massive rural–urban movements (20–30 million per year) occur: people are seeking better education, with 2.1 million students enrolled in educational institutions outside of their country of birth; there are better professional and working conditions particularly in the health sector contributing to the serious 'brain drain' of doctors and nurses; and then there is the increasing influence of diasporas, which maintain strong links with their country of origin, creating networks of migrants and establishing significant economic importance as well as encouraging further movements of people.

The migration process and health

Migrant populations are very heterogeneous in origin in terms of experienced exposures to risk factors, conditions of living in the host country and their access to healthcare services. Without doubt these many factors will influence their health status, and one way of looking at the health of migrants is to consider this in relation to the very process of migration itself [6].

The pre-departure phase is characterised by the influences upon health of the environment in which one individual or a group of migrants has lived. This refers to a broad spectrum of factors. One thinks immediately of the exposure to endemic diseases such as malaria, tuberculosis, intestinal parasites or viral hepatitis. Nutritional factors such as sufficient intake of micronutrients, vitamins and proteins will shape the nutritional status and normal growth of children. Social and economic factors such as poverty, illiteracy, unemployment, occupational hazards, poor housing and hygienic living conditions are among key factors shaping the future health status of migrants, as is the exposure to insecurity, war, violence, torture and other human rights violations. Religion and cultural background are of course of key importance in influencing health beliefs and behaviours. Finally, experiences encountered following contact with the medical services in the country of origin and with other traditional and lay medical providers will also influence a migrant's expectations and rapport with medical services in the country of settlement.

The journey itself may be very short and uneventful in the case of a routine flight to the new destination. But for many refugees and migrants the journey may be a long process, characterised by uncertainty, deprivation, insecurity, abuse, trauma and sometimes life-threatening events. This may be particularly the case for illegal migrants smuggled into a new country, and for women.

The receptive and resettlement phase may differ greatly according to the legal status of a particular person or community. The level of education, professional skills, language

and communication skills will influence the capacity of migrants to adjust to the new cultural, professional and social environment, and to progressively interact and integrate in the new society. Previous exposure to violence and trauma may pose a serious barrier to adaptation, as persons suffering from post-traumatic stress disorder (PTSD) may avoid contacts or over-react to new unexpected constraints or situations. Living conditions such as overcrowding or isolation may accelerate the transmission of diseases such as tuberculosis and varicella, or may have an important psychological impact. Restrictive policies aimed at discouraging newcomers to seek asylum may have also a deleterious effect on the mental health of asylum seekers or migrants [7]. The uncertainty about their future and the pending threat of deportation is also associated with negative consequences on mental health and interferes with the integration process in the host country. So do other restrictive policies, such as not allowing asylum seekers to work. Access to health services may be restricted. Nonetheless, arriving in the receiving country may be also a relief and give the opportunity to start a new life with access to services and better living conditions, which have a positive influence on the health of newcomers.

A return to their original home is being experienced by a growing number of migrants. This requires preparation, the re-establishing of previous links and contacts in order to readjust to a new life. For those returning to visit friends and relatives (VFR), health practitioners should raise their awareness about prevailing risks, particularly when travelling with children, and encourage them to seek pre-travel advice, vaccination and, where appropriate, malaria chemoprophylaxis.

When taking the successive steps of the migratory process into account, it is possible to build a clear view of the potential exposures and risk factors that may influence the present health condition of a specific person or community. This can help primary care providers to connect the present complaint or illness to previous events related to the migration process the person has undergone.

Thus the health of migrants is largely influenced by specific living conditions, previous exposure to communicable diseases, deprivation or violence, professional risks, the degree of integration into a new society, access to healthcare, the capability to communicate and the presence or absence of a community or family safety net. Presently, most of the data on migration and health come from surveys on specific groups of migrants or services, or through medical screening programmes at the time of entry into the host country. Routinely gathered data on the health of ethnic minorities or of foreign-born residents are often lacking in this area. Thus caution should be exercised in extrapolating the conclusions of specific studies to all migrants and in so doing, contributing to the negative perception of migrants and to an indirect form of discrimination.

From medical screening to access to care

International regulations, quarantine procedures and medical screening have been designed to control the spread of infectious diseases. At a time of worldwide mobility of millions of travellers, medical screening continues to be implemented for immigrants and refugees prior or at the time of entry to the receiving country. It is most frequently mandatory and in some instances it determines whether or not they will be accepted by the receiving country. Migrants may be afraid of such a medical examination that may hinder them from reaching their destination. Medical screening is aimed mainly at identifying communicable diseases such as tuberculosis, hepatitis B, syphilis, HIV or other health conditions that may cause a financial burden to the receiving country. Preventive measures such as vaccinations are often implemented at the time of screening and much of the data available on the health of migrants are drawn from medical screening at time of entry.

The diminishing impact of classical infectious diseases in a globally mobile world forces us to explore new approaches and responses. With mobile populations becoming a larger component of societies, infectious diseases with long periods of latency or those with subclinical or chronic stable infectious periods pose problems that are not solved by screening at the time of entry. Chronic infectious diseases such as tuberculosis, hepatitis B or C, schistosomiasis or infectious diseases with a long latency, such as vivax malaria, will often only be recognised after many months of residing in the host country. A good example is that of tuberculosis, where 52% of cases recorded in 2008 in migrants in the UK were detected more than 5 years after their arrival [8]. This shift towards the presence of chronic diseases creates a situation where the first interaction of a migrant or refugee with the healthcare system is likely to be at community level with primary care providers. This has direct implications for how and where to reinforce surveillance systems and the need to provide primary care doctors with adequate knowledge and training in recognising and managing diseases they may not be familiar with.

Health and diseases in migrants: a practitioner's perspective

Primary care providers and travel medicine professionals may frequently see migrants or refugees of various origins

both for treatment and for preventive measures such as immunisation. They need to be able to recognise diseases that are unusual and more 'exotic' than those prevalent in the local native population. They should also be aware of the long-term effects of exposure to violence, as many refugees and immigrants come from war-torn regions of the globe. They also need to develop a cultural competence to communicate with migrants and refugees and to be able to identify clearly their concerns, their health beliefs and how best to address their needs in a culturally sensitive manner.

Infectious diseases

Coming from regions where many cosmopolitan or tropical communicable diseases are more prevalent, a significant proportion of migrants may have been in contact with or infected with or indeed be a carrier of some specific infectious disease. This is particularly the case with tuberculosis.

Tuberculosis

Tuberculosis is a disease that is increasing worldwide due to population growth, as a co-infection of HIV and because of insufficient access to adequate treatment leading to the spread of resistant strains. Overall in North America and in Europe there has been a steady decrease in tuberculosis [9, 10], with much higher rates reported in the foreign-born population. In some European countries (UK, Sweden), an increase in the number of TB cases reported has been seen mainly in the foreign-born population. Annual incidence rates of TB in the UK in 2008 were 4.3 per 100,000 in UK-born and 87.5 per 100,000 in non-UK-born respectively. The median age in non-UK-born was 34 years, with the highest rate of disease reported in the 25- to 29-year age group (123 per 100,000). Less than 2% of new cases were multi-drug resistant. Pulmonary symptoms lasting more than 2 weeks, fatigue and weight loss should always raise the possibility of underlying tuberculosis. In migrants and refugees coming from countries where TB is endemic, a significant proportion of cases are extrapulmonary and should be looked for actively. In 2008, only 48% of non-UK-born cases demonstrated pulmonary TB compared with 71% of UK-born cases. The most common disease sites of extrapulmonary tuberculosis include lymph nodes, the muscoloskeletal system and the liver. Resistant strains of tuberculosis are emerging all over the world, including in industrialised countries. There has been a marked increase in the appearance of drug resistance in areas where access to treatment is inadequate and this is of particular concern in some East European countries. Cases of tuberculosis with a history of incomplete treatment are likely to be at a higher risk of developing drug resistance.

Viral hepatitis

Hepatitis A is highly prevalent in the developing world. In general, and by the age of 10, the vast majority of children have been exposed to hepatitis and develop lifelong protective antibodies. On some occasions, refugee children, some of whom have travelled while incubating the disease, have caused limited outbreaks in those persons with whom they have had close contact [11]. The epidemiology of hepatitis A is changing with the rapid urbanisation of the developing world and resulting in an increasing proportion of young migrants with no immunity to hepatitis A. In Asia and Africa, the endemicity of hepatitis B (HBV) is high, with more than 5% carriers of HBs antigen (HBsAg). The numerous screening surveys completed among immigrants and refugees demonstrate vast differences in the prevalence of HBV infection according to their country of origin [12]. The prevalence is highest in migrants coming from Southeast Asia/Pacific (3–24% HBsAg positive), Africa (7–9%) and Americas/Caribbean (1–14%), with lower rates in the Middle East (2–4%) and Eastern Europe/former Soviet Union (1–5%). Table 29.2 shows the seroprevalence of HBV in newly arrived refugees in Minnesota, US. This illustrates the variability due to the level of endemicity in their country of origin and also related to some selection factors inherent to the migratory process. Counselling and the provision of medical care to those who are chronically infected, together with the immunisation of relatives to prevent intrafamilial and infection of partners, should be undertaken by medical providers. Hepatitis C (HCV) is also of concern, with high prevalence rates (>10%) in the developing world, particularly in Egypt and sub-Saharan Africa, mostly due to unsafe injection practices.

Table 29.2 Health assessment for primary refugees in Minnesota

	Number	Tuberculine ≥ 10 mm)	HBsAg +	Parasites +
	n	%	%	%
Female	1,184	42.9	5.8	19.8
Male	1,360	53.7	8.8	23.4
0-6 years	280	13.7	2.9	24.3
7–17 years	886	37.6	6.6	31.3
18–50 years	1,161	62.3	9.0	15.5
≥51 years	218	63.6	7.4	13.8
Eastern Europe	585	42.8	4.4	9.7
Southeast Asia	83	51.3	2.9	29.5
Sub-Saharan Africa	1,869	50.5	8.5	25.1

Adapted from Lifson AR *et al*. 2002.

Malaria

Plasmodium falciparum malaria does not have a long incubation period. In the vast majority of cases, the disease becomes clinically apparent less than 1 month after an infective mosquito bite. For other types of malaria, such as *P. vivax, P. ovale and P malariae*, the latent phase can last for several months and even years after infection. Thus, a health practitioner should always consider malaria as a cause of fever in a migrant or refugee who originated from a tropical country. A study of newly arrived Liberian refugee children found the prevalence of malaria to be 60% (34/57) [13]. In the US, refugees coming from highly endemic countries now receive pre-departure treatment with antimalarials. In many European countries, an increasing proportion of cases of malaria is seen in migrants and refugees at the time of arrival from an endemic country or in ethnic minority travellers visiting friends and relatives (VFR). They often misperceive that having lived at their destination they have retained some immunity to infection with malaria, and therefore do not seek pre -travel health advice and do not take malaria chemoprophylaxis. There is some evidence that in more recent years imported malaria by VFRs from West Africa, one of the areas in which VFRs are most at risk of contracting malaria, is declining [14].

HIV/AIDS and sexually transmitted diseases

Asymptomatic infection with HIV is a consideration with migrants coming from regions where HIV/AIDS is endemic. In some countries, HIV testing is performed on all immigrants. Testing should be considered in those who may have risk factors (blood transfusion and multiple sexual partners among others). Voluntary screening, counselling, information on the disease and prevention should be encouraged in potentially at-risk groups. Access to therapy may be problematic, particularly for illegal migrants with no insurance coverage. Nevertheless, many migrants come from areas of the world where HIV/AIDS infection is less prevalent than in industrialised western countries and thus may be at higher risk of infection in their new host country. Targeted prevention programmes should be implemented at the time of arrival, while mandatory screening for HIV has often been considered unethical and discriminatory.

Sexually transmitted infections are on the rise in several countries. Testing for syphilis is still mandatory in order to enter some countries as a refugee or an immigrant. Sometimes a positive result may reveal a previous infection with an endemic treponematosis other than the sexually transmitted syphilis that is prevalent in many parts of the world.

Parasitic infections

Intestinal infection due to protozoa and helminthes is a very common finding in arriving migrants. The proportion of migrants infected varies significantly according to their country of origin. The prevalence in refugees of all ages migrating to Minnesota was 22% (462/2129) (see Table 29.2) [15]. Infection is mostly asymptomatic and some programmes have proposed systematic antihelminthic treatment with albendazol to be administered pre-departure or on arrival in the new host country with significant reduction in infection with both protozoa and helminthes; infection with the latter may last for years. Infection with helminthes may cause growth retardation and anaemia in children and should be screened for actively. Clinical presentation is often non-specfic, but the presence of eosinophilia should suggest screening for infection with helminthes. *Strongyloides sterchoralis* can be present for decades, causing a high eosinophilia count, cutaneous *larva currens* and pulmonary symptoms, with periodic auto-reinfection. Schistosomiasis can also persist for more than 20 years, causing potential local complications such as uretheral stricture, bladder fibrosis and possibly cancer. In migrants travelling from areas of hyperendemicity, haematuria may be considered a normal finding as it may be experienced by every child and so may not be reported. Several intestinal parasites are non-pathogenic and do not require any treatment (Table 29.3).

There are many other systemic parasitic diseases that physicians should be aware of; they should also be aware of their specific geographical distribution and relation to the migrant's origin and journey to the host country. These include: neurocysticercosis, which should be suspected in the case of seizures; echinococcosis; filariasis; onchocerciasis; paragonimiasis. *Strongyloides sterchoralis*, leishmaniasis and American trypanosomiasis should be looked for in case of organ transplant and/or immunosuppressive

Table 29.3 Gastrointestinal parasites

Pathogen	Non-pathogen
Giardia lamblia	*Endolimax nana*
Entamoeba histolytica	*Entamoeba coli*
Trichuris trichiuria	*Entamoeba dispar*
Ascaris lumbricoides	*Entamoeba hartmani*
Hymenolepsis nana	*Lodamoeba butschilii*
Hookworm	*Chilomastix mesnili*
Strongyloïdes stercoralis	*Blastocystis hominis (?)*
Schistosoma species	
Dientamoeba fragilis	

treatment being planned, they can reoccur in those who are immunocompromised and cause severe disease.

Chagas disease

Recently, American trypanosomiasis has attracted attention in migrants coming from Latin American countries in which it is endemic. In a recent study in Geneva, Switzerland, 12.8% (130/1012) of Latin American migrants tested positive for Chagas disease, with a total of 26.2% for the subgroup of 127 Bolivian migrants [16]. The disease is caused by *Trypanosomia cruzi*, a flagellated protozoa transmitted by a triatomine bug, and can remain asymptomatic for years with few or no circulating parasites. After several decades, 20 to 30% of those infected can develop cardiac or gastrointestinal complications. Chronic chagasic cardiopathy can cause severe morbidity and mortality. An electrocardiogram (ECG) is the recommended screening test for detecting cardiac damage, and frequently shows right bundle branch block. Blood-borne transmission has been also reported in non-endemic countries, leading to the screening of blood donors.

Eosinophilia

The most common cause of eosinophilia (absolute eosinophil count >450 cells/ml) observed in migrants is infection with helminthic parasites, presenting asymptomatically in the majority. In one study, eosinophilia was present in 12% (266/2224) of refugees from various parts of the world who had newly arrived in Boston, US. [17]. Pathogens were identified in stool samples of 29% (76/265) of refugees and serological testing was positive for *Strongyloides sterchoralis* in 39% (45/115), for *Schistosoma* species in 22% (15/67) and for filarial in 51% (18/35). It is recommended that when there is evidence of eosinophilia in newly arrived migrants, stool examination for parasites, serological examination for *S. sterchoralis*, *Schistosoma* species and filarial species should be undertaken for all migrants arriving from endemic areas.

Vaccine-preventable diseases

Migrants arriving in Europe and North America show great disparities in terms of health protection, including risk of infection with vaccine-preventable diseases. Some arrive with up-to-date immunisation records; many have no records or no clear recollection of previous vaccinations. Many come from countries where the risk of vaccine-preventable disease is higher than in the host country, the immunisation coverage rate is much lower and national programmes have not been fully implemented. They may, therefore, have already been exposed to communicable diseases such as measles and hepatitis A or B, and so present with long-lasting immunity or with no or insufficient protection against tetanus, diphtheria, polio or rubella. Several studies performed on immigrants to the US have shown large differences in the prevalence of antibodies to vaccine-preventable diseases [18]. In most receiving countries immunisation programmes are enforced to provide basic immunisation to all arriving immigrants and refugees. The cost-effectiveness of screening versus immunisation varies according to the diseases being considered. Screening for hepatitis B should always be undertaken in migrants from countries of high endemicity, while presumptive immunisation against polio, diphtheria and tetanus can be performed as screening increases the cost. It is worth remembering that a substantial proportion of migrants may not have benefited from organised immunisation programmes, therefore healthcare practitioners should always check and provide the complementary immunisations needed.

Other infectious diseases

The outbreak of meningococcal meningitis W135 that took place in Mecca in the spring of 2000 and the 2002–03 SARS epidemic, with imported cases and transmission to relatives and others in Europe and North America, reminds us that mobile populations can be at risk of and transmit infections, and demonstrates the importance of effective surveillance mechanisms. Migrants do not always import disease; they may arrive in European and North American countries not having been protected against common infectious diseases. This is the case with varicella, for example, a disease much less prevalent in certain tropical regions. Epidemics have been recorded in European countries [19], and immunisation should be considered, as varicella can be a very serious disease in unprotected adults.

Non-infectious diseases

Meeting the health needs of migrants requires identifying the presence of non-communicable diseases as well as infectious diseases. Chronic non-infectious diseases are of growing importance and pose difficult challenges for healthcare providers, including the promotion of changes in behaviour and ensuring adequate compliance with treatment in migrants of different cultural origin.

According to WHO, 60% of all deaths are due to chronic diseases and 80% of them occur in low- and middle-income countries [20]. Cardiovascular diseases, diabetes, asthma, respiratory diseases linked with smoking, cancers, occupational diseases and injuries, exposure to environmental hazards and mental disorders are on the rise in the

developing world as a result of rapid urbanisation, socioeconomic and behavioural changes. Surveys have shown that, as a result of lifestyle change, the incidence of cardiovascular diseases in populations of immigrants to Canada or the US tends to adjust with time to those observed in the local population [21]. Immigrants who were in the US for less than 1 year had a rate of obesity of 8%, which increased to 19%, close to the 22% rate for US-born children, after 15 years of residence [22]. In the UK, studies have shown that South Asian migrants have an elevated risk of ischaemic heart disease compared with Europeans and Afro-Caribbeans. These differences are mainly related to metabolic abnormalities (insulin resistance, hyperglycaemia and dyslipidaemia) that are more frequent in South Asians [23]. In the US, adolescent and adult immigrants have been found to be disproportionately affected by type 2 diabetes [24]. The aetiology seems to be multifactorial, involving both genetic and environmental factors. Migrants of African origin have been shown to be diagnosed with hypertension more frequently, with a tendency towards [25] type 2 (low renin) hypertension with a poor response to angiotensin-converting enzyme (ACE) inhibitors but a better response to calcium blockers and diuretics.

The frequency and the types of cancer vary significantly among geographic regions. While lung and breast cancer are the most common in men and women respectively worldwide, stomach and liver cancers in men, and cervical and colorectal cancers in women are more common in developing countries. According to WHO, more than 70% of deaths associated with cancer occur in low- and middle-income countries.

Epidemiological data on migrants should be integrated in a dynamic way as their migratory journey evolves. Healthcare practitioners should also look at the short- and long-term effect of protein or vitamin deficiencies leading to osteomalacia and bone deformation, iron deficiency and anaemia. Anaemia can also be a consequence of genetic traits such as G6PD deficiency or thalassemia. Both are quite frequent in ethnic minorities in England: 3–10% in Indians, 10–14% in Afro-Caribbeans and 20–25% in West Africans [26]. Oral health is an often forgotten problem of particular concern in children, who may show a high proportion of dental carries with long-term consequences.

This rapid overview of chronic non-communicable diseases should raise healthcare practitioners' awareness to this commonly overlooked dimension of migrant health. The geographical distribution of diseases and increased risk in specific migrant groups should always be considered. Prevention measures, counselling and providing sound health promotion advice, early disease detection and treatment can make a significant difference to the health of migrants.

Mental health and violence

The mental health of refugees and other migrants affected by conflicts has attracted a great deal of attention and become a priority for WHO [27]. Studies conducted both in the field and in countries of asylum have shown a high level of exposure to traumatic events, with an increased prevalence of some mental disorders, especially PTSD, compared with the general population. It is accepted currently that about one in 10 adult refugees in western countries has PTSD, with approximately one in 20 diagnosed with serious depression and about one in 25 diagnosed with a generalised anxiety disorder [28]. The overall prevalence rates of major depression in refugees may be similar to those in several general western populations, but co-morbidities and overlap between mental disorders, including serious depression, appear to be more frequent [29]. Large differences in the rates of PTSD and depression have emerged from epidemiological surveys. Apart from methodological differences among studies, exposure to torture is the most important source of variance in both depression and PTSD rates [30]. There is still much debate on the validity of western classification systems of mental disorders such as the DSM-IV and the ICD-10 across the cultural diversity of societies from various origins. The pitfalls of medicalisation normal distress are of special concern [31].

Treatment of traumatised refugees should include the range of interventions that have proved to be effective for PTSD and depression, including pharmacotherapy and psychotherapy. However, the absence of meeting basic needs such as protection following a threat to a person's life, a secure residence, employment and cultural adjustment sometimes compromises traditional psychotherapeutic interventions. There are very few reports on the results obtained following psychotherapy [32]. To bridge cultural gaps, specific interventions have been proposed, such as multiple family group interventions and, when appropriate, collaborative work with traditional healers [33].

Healthcare practitioners should be aware of possible previous exposure to war, torture or other trauma and its impact on health. Recognising physical and psychological symptoms related to rape, various forms of physical abuse, PTSD or depression, including how they are being expressed in a specific society or ethnic group, are of prime importance. Very often victims of organised violence will not present to healthcare practitioners as such, but will present with common non-specific symptoms such as headache, fatigue and general pain. It is only when trust, confidence and empathy are established, when the patient feels that the physician or the nurse are open to listening, that they will talk about their traumatic experiences and then allow for the therapeutic process to start.

Table 29.4 A few questions to elicit the patient's explanatory model

1 What do you (or other people) think has caused your problem?
2 Why do you think it started when it did?
3 What do you think your sickness does to you?
4 How severe is your sickness? Will it have a short or long course?
5 What kind of treatment do you think you should receive?
6 What are the most important results you hope to receive from this treatment?
7 What are the chief problems your sickness has caused for you?
8 What do you fear most about your sickness?

Adapted from Kleinman 1978.

Acquiring cultural competence

As medical providers and travel medicine doctors are caring increasingly for patients of diverse sociocultural backgrounds, it is essential to acquire cultural competence. Patient satisfaction and compliance with medical recommendations and treatment are closely related to the effectiveness of communication and the quality of the patient–doctor relationship. Physicians need to understand how each patient's sociocultural background affects their health beliefs and behaviour. Much work has already been done in proposing ways for doctors to recognise cultural differences and to understand better how patients perceive and experience their health condition or illness.

> *Eliciting the patient's (explanatory) model gives the physician knowledge of the beliefs the patient holds about his illness, the personal and social meaning attached to his disorder, his expectations about what will happen to him and what the doctor will do, and his own therapeutic goals. Comparing the patient model with the doctor's model enables the clinician to identify major discrepancies that may cause problems for clinical management* [34].

Acknowledgement and discussion of differences and similarities between the two models leads to a negotiation process that will help in reaching a satisfactory solution. A set of questions helping the clinician to elicit the patient model is given in Table 29.4. Language barriers may be such that working with interpreters and bilingual cultural mediators may be a necessity. Effective communication between the practitioner and the patient is essential. Patients with limited language proficiency in the host country should have access to bilingual providers or trained interpreters. This will lead to optimal communication, improve satisfaction of both patients and health professionals, and provide better outcomes and fewer errors with potential clinical consequences [35]. Interpreters can play a central role in helping medical providers to understand cultural differences that should be taken into account in the management of patients. Healthcare practitioners need to acquire some competencies in working with interpreters [36].

Table 29.5 Core cross-cultural issues

Styles of communication
Mistrust and prejudice
Decision making and family dynamics
Traditions, customs and spirituality
Sexual and gender issues

Adapted from Green AR *et al*. 2007.

To develop cultural competence, medical providers need to integrate health-related beliefs and cultural values, disease incidence and prevalence, and treatment efficacy. To enable an understanding of the patient model and expectations, an epidemiological perspective, as illustrated above for refugees and migrants of different origin, should be included. In modern diverse societies, learning about all the characteristics of the various cultures is impossible and may lead to assumptions and stereotypes. A patient-based approach that focuses on the issues that arise commonly due to cultural differences and how they impact interaction with any patient will allow a healthcare practitioner to explore for each individual patient, the core issues that influence their health and current needs [37]. Table 29.5 summarises the core cross-cultural issues.

Caring for patients: a patient-based approach

Over the past few decades global mobility has reshaped the practice of medicine. Healthcare practitioners regularly see patients who travel abroad or return with diseases contracted overseas. Furthermore, an increasing proportion of their patients are of diverse origins. Migration medicine – the medical skills required to provide adequate care and respond to the patient's needs, which may be diverse in origin – is becoming a regular part of the practice of medicine, including that of travel medicine. Initially only doctors and nurses working in specialised clinics established for newly arrived immigrants and refugees were involved in this specific provision of healthcare.

As our societies diversify and become more cosmopolitan, caring for migrants is inevitably a more common and generalised aspect of practice for healthcare practitioners. Many migrants from undeveloped countries may have a higher prevalence of infectious diseases such as tuberculosis, intestinal parasites or hepatitis B. They may be more prone to diabetes or hypertension due to genetic determinants or linked to specific nutritional and cultural habits. Healthcare practitioners need to know about these characteristics and be aware of the epidemiology and clinical manifestations of diseases they may not be familiar with. More important is the set of core values that should guide their practice.

Communication difficulties, uncertainties about the real needs of the patient, the administrative and financial constraints related to the status of the migrant, and previous traumatic experience that may impair the patient–doctor relationship are all factors that may lead to misunderstanding and frustration on the part of the doctor and the patient. This often reflects inherent differences in cultural values and expectations. It may translate into mistrust, or lack of understanding and compassion. As AR Green and JR Betancourt stated: 'at the heart of any meaningful and successful medical encounter (especially across cultures) there are three core values: empathy, curiosity and respect' [38]. Of course this triad applies to all patients, not just to migrants, but it is crucial to respect it in cross-cultural practice where differences may be more profound and may have a negative influence on the patient–doctor relationship. Learning, understanding and responding to the patient's feelings and needs are essential. This process is fascinating as we discover the life and the experiences encountered by an individual in an environment that is unique, provided trust and respect are experienced by both the patient and doctor. A patient-based approach is at the centre of any medical encounter. Taking the time to learn from the patients themselves about their cultures and their belief allows an understanding of their needs and avoids the risk of stereotyping.

Without doubt health services need to provide an adequate environment to promote cultural competence. They have to become more sensitive to and inclusive of a migrant's needs, and avoid setting up parallel migrant-specific services outside the mainstream [2]. Existing health inequities and barriers to accessing health services need to be reduced and governments should move from an exclusive to an inclusive approach to migrant health.

References

1. International Organisation for Migration (2009) Global Estimates and Trends, http://www.iom.int/jahia/Jahia/about-migration/facts-and-figures/global-estimates-and-trends (accessed 15.07.12).
2. World Health Organization (2010) Health of Migrants – the Way Forward. Report of a Global Consultation. Madrid, Spain, 3–5 March 2010. WHO, 2010, http://www.who.int/hac/events/consultation_report_health_migrants_colour_web.pdf (accessed 15.07.12).
3. UNHCR (2009) Global Trends: refugees, Asylum Seekers, Returnees, Internally Displaced and Stateless Persons. 15 June 2009, http://www.unhcr.org/cgibin/texis/vtx/search?page=search&docid=4c11f0be9&query=2010%20global%20trends (accessed May 10, 2010).
4. US State Department (2006) Trafficking in Persons Report 2006. Washington, http://www.state.gov/g/tip/rls/tiprpt/2006 (accessed 15.07.12).
5. Le Monde (2008–2009) *Atlas des migrations, hors série*. Edition le Monde, Paris.
6. Gushulak B and MacPherson D (2006) *Migration Medicine and Health. Principles and Practice*, BC Decker Inc, Hamilton.
7. Robjant K *et al.* (2009) Mental health implications of detaining asylum seekers: systematic review. *BrJ Psychiat* **194**(4): 306–312.
8. Health Protection Agency (2009) Tuberculosis in the UK: annual report on tuberculosis surveillance in the UK 2009. Health Protection Agency Centre for Infection, London.
9. CDC (2009) Trends in tuberculosis – United-States 2008. *MMWR: Morbid Mortal Wkly Rep* **58**(10): 249–253. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5810a2.htm (accessed 17 July 2012).
10. Hollo V *et al.* (2009) Tuberculosis in the EU and EEA/EFTA countries – What is the latest data telling us. *Eurosurveillance* **14**(11): pii=19151.
11. Castelli F *et al.* (1999) Pediatric migration and hepatitis A risk in host population. *J Travel Med* **6**: 204–206.
12. Armstrong GL and Goldstein ST (2007) Hepatitis B: global epidemiology, diagnosis and prevention. In: Walker PF and Barnett ED (eds) *Immigrant Medicine*, pp. 321–341. Saunders – Elsevier, Philadelphia, USA.
13. Maroushek SR *et al.* (2005) Malaria among refugee children at arrival in the United States. *Pediatr Infect Dis J* **24**: 450–452.
14. Behrens R *et al.* (2008) Declining incidence of malaria imported into the UK from West Africa. *Malar J* **7**: 235.
15. Lifson AR *et al.* (2002) Prevalence of tuberculosis, hepatitis B virus and intestinal parasitic infections among refugees to Minnesota. *Public Health Rep* **117**: 69–77.
16. Jackson Y *et al.* (2010) Prevalence, clinical staging and risk for blood-borne transmission of Chagas disease among Latin American migrants in Geneva, Switzerland. *PLoS Negl Trop Dis* **4**(2): 592.
17. Seybolt LM *et al.* (2006) Diagnostic evaluation of newly arrived asymptomatic refugees with eosinophilia. *Clin Infect Dis* **42**(3): 363–367.
18. Barnett ED (2007) Immunizations for immigrants. In: Walker PF and Barnett ED (eds) *Immigrant Medicine*, pp. 151–170. Saunder–Elsevier, Philadelphia, USA.
19. Kjersem H and Jepsen S (1990) Varicella among immigrants from the tropics, a health problem. *Scand J Soc Med* **18**: 171–174.
20. World Health Organisation (2005) Preventing Chronic Diseases, A Vital Investment. WHO Geneva, Switzerland, http://www.who.int/chp/chronic_disease_report/full_report.pdf (accessed 15.07.12).
21. Kliever E (1992) Epidemiology of diseases among migrants. *Int Migr* **30**: 141–165.

22. Goel MS *et al.* (2004) Obesity among US immigrant subgroups by duration of residence. *JAMA: J Am Med Assoc* **292**(23): 2860–2867.
23. Tillin T *et al.* (2005) Metabolic syndrome and coronary heart disease in South Asians, African-Carribbeans and white Europeans: a UK population-based cross-sectional study. *Diabetologia* **48**(4): 649–656.
24. Egede LE and Dagogo-Jack S (2005) Epidemiology of type 2 diabetes: focus on ethnic minorities. *Med Clin North Am* **89**(5): 949–975, viii.
25. Brown MJ (2006) Hypertension and ethnic groups. *Br Med J* **332**: 833–836.
26. Modell M and Modell B (1990) Genetic screening for ethnic minorities. *Br Med J* **300**: 1702–1703.
27. Brundtland GH (2000) Mental health of refugees, internally displaced persons and other populations affected by conflict. *Acta Psychiatr Scand* **102**: 159–161.
28. Fazel M *et al.* (2005) Prevalence of serious mental disorder in 7000 refugees resettled in western countries: a systematic review. *Lancet* **365**(9467): 1309–1314.
29. De Jong JT *et al.* (2003) Common mental disorders in postconflict settings. *Lancet* **361**(9375): 2128–2130.
30. Steel Z *et al.* (2009) Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass conflict and displacement: a systematic review and meta-analysis. *JAMA: J Am Med Assoc* **302**(5): 537–549.
31. Summerfield D and Veale D (2008) Proposals for massive expansion of psychological therapies would be counterproductive across society. *Br J Psychiatry* **192**(5): 326–330.
32. Cloitre M (2009) Effective psychotherapies for posttraumatic stress disorder: a review and critique. *CNS Spectr* **14**(1 Suppl. 1): 32–43.
33. Jones L *et al.* (2009) Severe mental disorders in complex emergencies. *Lancet* **374**(9690): 654–661.
34. Kleinman A *et al.* (1978) Culture, illness, and care. Clinical lessons from anthropologic and cross-cultural research. *Ann Intern Med* **82**: 251–258.
35. Flores G (2005) The impact of medical interpreter services on the quality of healthcare: a systematic review. *Med Care Res Rev* **62**: 255–299.
36. Bischoff A and Loutan L (2008) Other Words, Other Meanings: a Guide to Health Care Interpreting in International Settings, http://medecine-internationale.hug-ge.ch/eng/ (accessed July 23, 2012).
37. Carillo JE *et al.* (1999) Cross-cultural primary care: a patient-based approach. *Ann Intern Med* **130**: 829–834.
38. Green AR and Betancourt JR (2007) Cultural competence: a patient-based approach to caring for immigrants. In: Walker PF and Barnett ED (eds) *Immigrant Medicine*, pp. 83–97. Saunders–Elsevier, Philadelphia, US.

Chapter 30 Visiting friends and relatives

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Introduction

Travel medicine has traditionally focused on tourist and business travellers, but increasingly immigrants and their families returning to their home countries, often to visit family and friends still resident there, are becoming an important population. For want of a better term, this population has been labelled 'visiting friends and relatives' or VFRs. VFRs have been identified in travel and tourism markets as a distinct group of travellers who have different risk factors in terms of travel-related healthcare. This population has been identified because often thei needs are not met and challenges exist as to how they may potentially be targeted so that pre- and post-travel healthcare may be provided.

The number of people travelling internationally is increasing every year. According to the World Tourism Organisation, international tourist arrivals in the year 2009 reached 880 million, with 27% motivated by travel for other purposes, such as VFR, religious reasons/pilgrimages, health treatment, etc. [1]. Of ill returned travellers identified through 30 GeoSentinel sites in six continents, VFRs represent 8–24% of all travellers, with sub-Saharan Africa having the highest proportion [2]. Around 175 million people currently reside in a country other than where they were born, which is about 3% of the world population. The number of migrants has more than doubled over the past 30 years. In spite of being a minority of the population, VFRs comprise 40% of international travellers, including to Africa. While the reason for travel is broadly known, there may be distinct differences from other travellers with respect to exposures. Health and cultural beliefs may also be different and these may influence uptake of pre-travel interventions. An example of this is the perception of immunity to malaria even after prolonged residence in a non-malaria-endemic region. This perceived immunity may also be extended to other family members, particularly children who are believed to have acquired immunity from their parents despite having been born and lived most of their lives out of the countries of origin of their parents. Cultural and language barriers may also be important factors with regards to engagement with healthcare, including travel-related health. Social and financial factors may also be relevant issues affecting VFR travellers more so than other travellers.

Who are VFR travellers?

The travel and tourism industry first recognised and developed the concept of travel for the purpose of 'visiting friends and relatives' as distinct from those travelling for tourism, business or long-term travel [3]. Although VFR travellers were identified as a distinct population, they were felt to be difficult to influence and therefore of minor economic impact for the travel industry. Furthermore, there was no clear and focused definition for this group, which has meant that this population is underestimated and neglected in terms of the travel industry [4]. The term VFR was then adopted by travel medicine experts who identified VFRs as a distinct group of travellers who faced different and sometimes higher risks for morbidity and mortality than conventional travellers. However, again there has been no standardised and focused definition for VFRs, but the term has been used broadly to cover ethnic travellers who have immigrated at some period in the past and maintain family links in their country of origin [5]. Included in the VFR category are family members, such as spouses and children, who were born in the country of residence but are travelling as a family unit for purposes of visiting friends and relatives. Due to the lack of a standardised definition, studies and publications on VFRs have used varied terminology, which makes comparisons difficult. Furthermore, additional qualifiers have been introduced, such as 'immigrant VFR' and

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'traveller VFR', in an attempt to define VFRs better [6]. VFR travellers are also not a homogeneous group and may include children of foreign-born parents, i.e. second-generation immigrants whose family originated in the country visited. It is not clear when immigrant communities who have lived away from their countries of origin for several generations stop being VFRs. There may be specific risk differences within countries or geographical regions that do not require immigration in the formal sense but do nevertheless pose health risks to those individuals.

In view of that fact that global motility of populations has increased, definitions based on immigration no longer apply. It has also been felt that the classical definition of VFR traveller no longer applies to many travellers who may have risks of travel-related illness, which are similar to those experienced by the classic VFR traveller. Recently, an expert committee of the International Society of Travel Medicine has suggested a new definition for VFR travellers which aims to overcome some of the shortfalls of the classic definition [7]. A revised definition and framework has been proposed and includes two key components:

- the intended purpose of travel is to visit friends or relatives
- there is an epidemiologic gradient of health risk between the two locations supported by an assessment of health determinants.

The gradient of health risks takes into account risk for both infectious (infectious and tropical diseases, sexually transmitted infections) and non-infectious conditions (road and travels hazards, crime and violence, illegal drugs, climate and environment). Closely linked to this gradient are determinants of health, including socioeconomic factors, behavioural factors, genetic and biological factors, and environmental factors. It is proposed that travel medicine practitioners use this new framework as part of pre-travel assessment. However, it has been suggested that a more inclusive definition will result in greater numbers of travellers classified as VFRs, and that the creation of an even more heterogeneous VFR category may make it difficult to tease out underlying reasons for the higher-risk behaviours [8]. Furthermore, changing the definition of VFR travellers does not necessarily help identify the issues relating to lack of uptake of pre-departure interventions in this population.

What are the VFR traveller's risks?

VFR travellers living in resource-rich countries cross more than just national boundaries; they often cross the healthcare divide too. While earlier immigration was due to escaping inhospitable conditions at home, more recent immigration has been for employment or family reunification [9]. In addition to these factors, affordability of air travel, and fewer socioeconomic and political obstacles have meant that VFR travel has become increasingly more common, albeit with increased and new risks.

Because of the characteristics associated with their travel, VFR travellers going to developing countries are commonly considered at higher risk for illness than tourists going to those countries. VFRs are more likely to travel to rural destinations, have longer durations of stay and make multiple visits. Dietary and water sources may also be different to those of tourists and may include untreated water and uncooked foods. There may also be closer contact with local residents, as in most cases VFR travellers will reside with family members. Exposure to diseases prevalent in those communities is therefore more likely due to nature of contact, which may be close and prolonged (e.g. respiratory tract infections, tuberculosis). While infectious risks are among the commonest problems encountered by VFR travellers, non-infectious risks, such as road traffic accidents and crime, are also hazards that VFR travellers may face and they will be different to those of other travellers due to the nature of their travel.

Malaria

Malaria is the most serious infectious risk to all travellers in many parts of the world. Of ill returned travellers identified through 30 GeoSentinel sites in six continents, malaria was the most frequent cause of systemic febrile illness [2]. In Europe, a TropNetEurop study of imported falciparum malaria showed that 48% of cases were in semi-immune immigrant travellers and 54% in VFR travellers [10]. In the UK, VFR travellers accounted for 78% of imported malaria in 2007, with more than 80% of cases being due to falciparum malaria [11]. Eighty-seven per cent of VFR cases were of Black African ethnicity or descent and had travelled to countries or regions of their ethnic origin. A retrospective analysis of imported malaria in children in the UK from 1999 to 2003 showed that 60% of cases were in VFR travellers [12]. There was a bimodal seasonal distribution observed, with a large peak in July and August, reflecting travel during the summer school holidays. Children travelling on holiday were more likely to take malaria prophylaxis compared with VFR children (56.9% versus 37.4%). In a smaller retrospective review of malaria in children in east London, almost a quarter of children with malaria had another family member also diagnosed with malaria, most often either a sibling or a parent [13]. These data would suggest that VFRs are often travelling together as family units for prolonged periods and often without any preventative measures.

Typhoid and paratyphoid (enteric fever)

Most reports of typhoid and paratyphoid in developed countries are related to travel, most commonly to the Indian subcontinent (ISC), which accounts for 37–91% of cases [14, 15]. In the UK, 88% of travel-associated cases of enteric fevers involved VFR travel. Only 43% of VFR cases had sought health advice pre-travel, compared with 61% of non-VFR travellers [11]. Uptake of vaccine was also low in this population.

Hepatitis A

In the UK, travel-associated hepatitis A accounts for up to 10% of all cases notified, although this proportion has been declining as have the total numbers of cases reported [11]. The ISC has traditionally been the region of travel most reported for travel-associated hepatitis. Higher rates of hepatitis occur in people of south Asian ethnicity, and travelling 'home' to the ISC to visit friends and relatives was a significant risk factor [16]. In a study by Behrens *et al.*, children under the age of 15 years from VFR families travelling to the ISC appeared to be twice as likely to develop symptomatic hepatitis than older travellers. In the same study, ethnic travellers were eight times more likely to develop hepatitis A than tourists or other travellers [17]. In a study from the Netherlands, paediatric hepatitis A notifications peaked in autumn months, presumably following return from summer holidays in predominantly Turkish and Moroccan children [18].

Tuberculosis

In 2008, there were an estimated 11.1 million prevalent cases and 9.4 million new cases of tuberculosis (TB) globally, mostly in developing countries (Asia 55%, Africa 30%) [19]. HIV has exacerbated the tuberculosis epidemic globally especially in Africa, where up to 70% of people with tuberculosis are also HIV positive [20]. International migration and travel have also resulted in a resurgence of TB in some industrialised countries, which have witnessed an overall increase in TB with a significantly greater proportion of cases in foreign-born individuals. In the UK for example, notification rates in non-UK born individuals were almost 20 times greater than in UK-born individuals (87 versus 4 cases/100,000 notifications). Notification rates were higher in some ethnic groups, such as non-UK-born Black Africans (314 cases/100,000 population), which persisted even in those who were born in the UK (53 cases/100,000 population) [21].

The relationship between acquisition of TB and VFR travel is more difficult to ascertain. TB transmission is more likely to occur following prolonged (>8 hours/day) and close (usually household) contact and this would be very much the sort of contact VFR travellers would encounter in contrast to tourists. Ormerod *et al.* have shown that of ISC ethnic travellers developing TB disease, 66% had reported a visit to the ISC within 3 years of notification, including 60% of UK-born individuals without prior exposure to the ISC [22]. Similarly, others have shown that the incidence rates of *Mycobacterium tuberculosis* infection and of active disease were 3.5 per 1,000 person-months of travel (2.0–6.2) and 0.6 per 1,000 person-months of travel (0.3–2.3) respectively [23]. Bottieau *et al.* showed that of those returned travellers with fever, 1% (13% in those with HIV infection) were found to have TB [24]. However, several other factors, such as frequency of travel and visits from relatives from high prevalent countries, may also contribute to higher rates in the VFR population. In a case-control study of children <6 years of age with positive tuberculin skin tests, children who had travelled in the 12 months before their tuberculin skin test were 3.9 times more likely to have a positive test than children who had not travelled. More than half of the children were visiting their grandparents during their travel. However, children who had a household visitor from a country with high TB prevalence were 2.4 times more likely to have a positive tuberculin skin test than were those who did not have a visitor [25].

Vaccine-preventable infections

At present there are limited data on the risk of common vaccine-preventable infections, such as measles, mumps and polio, in VFR travellers. These infections are all more prevalent in countries visited by VFRs. Furthermore, due to lower rates of vaccination coverage in VFR communities, this population – especially children – may be at particular risk from these vaccine-preventable infections.

HIV and STIs

It has been estimated that the relative risk of HIV infection in black African adults is 20 times, and for children 355 times, higher than in non-African equivalents in the UK [26]. Similarly, rates of STIs, such as gonorrhoea, are significantly higher in Afro-Caribbean men than in the white population. Bottieau *et al.* showed that in those returned travellers with fever, 2% (9% in those with HIV infection) had evidence of an STI [24].

Emerging infections

While most travel-related infections that VFRs encounter will be well established or exist at varying levels within the

areas visited, there will also be newly emergent and novel infections that will impact on VFRs more so than other travellers. The severe acute respiratory syndrome (SARS) outbreak in 2003 highlights the ease and rapidity with which a newly emerged coronavirus infection can spread to cause a global outbreak, with more than 8,000 cases worldwide involving 30 countries [27]. SARS was initially carried out of the Guangdong Province in China by a medical doctor who stayed in a hotel in Hong Kong, where he was visiting his family. A total of 1,755 cases of SARS were subsequently diagnosed in Hong Kong, of which 295 (16.8%) died. SARS was introduced to Toronto by a woman of Hong Kong descent who had travelled home to visit relatives and had stayed at the same hotel in Hong Kong as the medical doctor from Guandong Province [28]. While this outbreak was not limited to VFR travellers, it highlights not only the risks that VFR travellers face but also the importance that VFRs play in transmission of infection. This outbreak also identifies the difficulties that exist with VFR definitions that may be more fluid in outbreak situations.

More recently, there has been a major outbreak of Chikungunya virus in the islands of the Indian Ocean reported in 2006 and subsequently in India and Southeast Asia in 2007. Imported cases have occurred, including in VFR travellers [29]. In 2007, transmission was reported for the first time in Europe, in a localised outbreak in Italy [30]. The index case was a man of Indian origin living in Italy who had not travelled but had reported that he had been visited by a relative from India, who serologically had evidence of Chikungunya. Subsequently 205 cases occurred in one region in Italy.

What are the barriers to pre-departure care?

Angell and Cetron have identified barriers that exist for VFR travellers with regard to pre-departure care [9]. They include the following.

- Systems level
  - lack of insurance coverage and no primary care provider
  - travel clinics considered 'non-essential care' and not covered by insurance
  - travel medicine clinics developed around tourist industry and not integrated into patient's longitudinal or generic healthcare services
  - incomplete routine childhood immunisations and lower rates of immunisations in VFRs, including children.
- Provider level
  - primary care physicians have competing priorities for regular healthcare visits
  - inadequate knowledge and training in travel medicine (inappropriately prescribed medications)
  - unclear national guidelines/recommendations.
- Traveller level
  - lower perception of risk or threat by traveller
  - cultural and ethnic differences
  - VFR travellers less likely to seek pre-travel advice and less likely to adhere to recommended medications and travel precautions interventions
  - reasons for travel may be different, including emergency travel.

Strategies to reduce VFR-related barriers to care

Having identified the barriers to pre-departure care above, it will no doubt be important to determine the factors that lead to poor uptake of interventions and also lack of engagement with established pre-departure healthcare providers. In light of racial, cultural and ethnic differences experienced by VFR populations, it will be important to eliminate, or at least overcome, some of these in order to improve access to healthcare. Language and culturally appropriate information should be provided to VFR communities highlighting the risks they face and also the interventions that are available to them. Accessing the VFR community through radio stations and church groups have been methods used to provide information. In light of the fact that many VFRs are travelling as family units and during the summer school holidays, targeting school children prior to their summer holidays may be one strategy to provide information and access to travel medicine clinics. Furthermore, providing access to travel clinics located within generic health services/primary care may be an important development. Finally, financial assistance and support may be important in overcoming some of the financial constraints faced by many VFRs. Novel approaches for delivering pre-departure healthcare for VFRs needs to be explored.

Conclusions

A distinct and previously under-reported group of travellers, known as VFRs, has been increasingly recognised as a sizeable and growing population consistent with overall global trends in migration and travel. While definitions and risk factors remain ill-defined, VFRs have a disproportionate burden of infectious diseases, such as malaria, typhoid and tuberculosis. Identifying both risk factors and the barriers to access for pre-travel healthcare will no doubt be important in formulating strategies and interventions. A paradigm shift

in travel healthcare provision will be needed to address the needs of the VFR traveller.

References

1. *UNWTO World Tourism Barometer* (2010) 8: 1–60.
2. Freedman DO *et al.* (2006) Spectrum of disease and relation to place of exposure among ill returned travellers. *N Engl J Med* **354**: 119–130.
3. Jackson RT (1990) VFR tourism: is it underestimated? *J Tourism Stud* **1**: 10–17.
4. Backer E (2007) VFR travel: an examination of the expenditures of VFR travellers and their hosts. *Curr Issues Tourism* **10**: 366–377.
5. Keystone JS (2010) VFRs: immigrants returning home to visit friends and relatives. In: Brunette GW *et al.* (eds) *Health Information for International Travel*, pp. 547–551. Center for Disease Control and Protection, Atlanta, GA.
6. Leder K *et al.* (2006) Illness in travellers visiting friends and relatives: a review of the GeoSentinel Surveillance Network. *Clin Infect Dis* **43**: 1185–1193.
7. Barnett ED *et al.* (2010) The visiting friends or relatives traveller in the 21st century: time for a new definition. *J Travel Med* **17**: 153–162.
8. Arguin PM (2010) A definition that includes first and second generation immigrants returning to their countries of origin to visit friends and relatives still makes sense to me. *J Travel Med* **17**: 147–149.
9. Angell SY and Cetron MS (2005) Health disparities among travellers visiting friends and relatives abroad. *Ann Intern Med* **142**: 67–72.
10. Jelinek T *et al.* (2002) Imported falciparum malaria in Europe: sentinel surveillance data from the European network on surveillance of imported infectious diseases. *Clin Infect Dis* **34**: 572–576.
11. Health Protection Agency(2008) Foreign travel-associated illness – a focus on those visiting friends and relatives 2008 report. Travel and Migrant Health Section, Health Protection Agency, December 2008.
12. Ladhani S *et al.* (2006) Trends in imported childhood malaria in the UK: 1999–2003. *Arch Dis Child* **91**(11): 911–914.
13. Ladhani S *et al.* (2003) Childhood malaria in East London. *Pediatr Infect Dis J* **22**(9): 814–819.
14. Lighton LL (1999) Follow up in Northwest England of cases of enteric fever acquired abroad. *Commun Dis Pub Health* **2**: 145–146.
15. Mermin JH *et al.* (1998) Typhoid fever in the United States, 1985–1994: changing risk of international travel and increasing antimicrobial resistance. *Arch Intern Med* **158**: 633–638.
16. Gungabissoon U *et al.* (2007) Hepatitis A virus infection in people of South Asian origin in England and Wales: analysis of laboratory reports between 1992 and 2004. *Epidemiol Infect* **135**(4): 549–554.
17. Behrens RH *et al.* (1995) Risk of British travellers acquiring Hepatitis A [letter]. *Br Med J* **311**: 193.
18. Termorhuizen F and van de LAar MJ (1998) The epidemiology of Hepatitis A in the Netherlands, 1957–1998. *Ned Tijdschr Geneeskd* **142**: 2364–2368.
19. WHO (2009) Global Tuberculosis Control: a Short Update to the 2009 Report, http://www.who.int/tb/publications/global_report/2009/en/index.html (accessed 31 May 2010).
20. Ghebreyesus TA *et al.* (2010) Tuberculosis and HIV: time for an intensified response. *Lancet* **375**: 1757–1758.
21. Health Protection Agency(2009) Tuberculosis in the UK: Annual report on tuberculosis surveiilance in the UK 2009. London Health Protection Agency Centre for Infections, December 2009.
22. Ormerod LP *et al.* (2001) Are there still effects on Indian subcontinent ethnic tuberculosis on return visits? A longitudinal study 1978–97. *J Infect* **43**: 132–134.
23. Cobelens FG *et al.* (2000) Risk of infection with *Mycobacterium tuberculosis* in travellers to areas of high tuberculosis endemicity. *Lancet* **356**: 461–465.
24. Bottieau E *et al.* (2008) Fever after a stay in the tropics: clinical spectrum and outcome in HIV-infected travellers and migrants. *J Acquir Immune Defic Syndr* **48**: 547–552.
25. Lobato MN and Hopewell PC (1998) *Mycobacterium tuberculosis* infection after travel to or contact with visitors from countries with a high prevalence of tuberculosis. *Am J Respir Crit Care Med* **158**: 1871–1875.
26. De Cock KM and Low N (1997) HIV and AIDS, other sexually transmitted diseases, and tuberculosis in ethnic minorities in United Kingdom: is surveillance serving its purpose? *Br Med J* **314**: 1747.
27. Peiris JS *et al.* (2003) Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* **361**: 1319–1325.
28. Poutanen SM *et al.* (2003) Identification of acute severe respiratory syndrome in Canada. *N Engl J Med* **358**: 1995–2005.
29. Lim PL *et al.* (2009) Chikungunya in Singapore: imported cases among travellers visiting friends and relatives. *J Travel Med* **16**: 289–291.
30. Rezza G *et al.* (2007) Infection with chikungunya virus in Italy: an outbreak in a temperate region. *Lancet* **370**: 1840–1846.

Chapter 31 Travel medicine, ethics and health tourism

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HEALTH TOURISM

Introduction

'Health tourism' may be loosely defined as travel for the purpose of obtaining healthcare. This may or may not involve crossing an international border. In its modern context, it typically involves a quest for non-critical, elective rather than emergency care, and the purpose is frequently for one-off treatment – such as a surgical procedure or an expert opinion – rather than for the ongoing management of chronic disease.

Travellers who fall victim to illness or injury in the course of their travels are clearly excluded from this definition: they are not health tourists, though many of the issues they face are undoubtedly the same.

Travellers may become unintentional health tourists when they buy local medicines, or try out local therapies and treatments, without this being the primary purpose of their trip.

Historical background

Health tourism is not new. From the earliest times, people have travelled great distances in search of cures, a notion that was commonplace to the ancient Greeks and Romans, and one that is a recurring theme in the Old and New Testaments.

Spas and places linked historically with healing can be found across Europe, attracting health seekers and therapists alike. In England, for example, the discovery of the rejuvenating properties of the Chalybeate Spring in 1606 by a young nobleman, Lord North, led to the creation of the spa town of Royal Tunbridge Wells, which reached the height of fashion, popularity and patronage in the eighteenth century [1]. Its reddish waters offered the prospect of a cure from 'obstructions, especially of the spleen and liver; dropsy, jaundice, scurvy, the green sickness, defect and excess of female courses, inward inflammations and hot distempers, palsy, apoplexy, rheums, hypochondriacal melancholy, pox, pimples and other external infirmities; the waters scoureth and cleanseth the urinary passages… and nothing is better against barrenness'. Contemporary medicine had little else to offer against such ailments, and any health benefits probably arose from the water's high iron content. At around the same time, the purgative effects of the waters of Epsom led to the creation of another popular spa, as high society flocked there to take the waters – rich in magnesium sulphate, a substance that is still often referred to as 'Epsom salts'.

Holy places have also offered the prospect of a cure, and even today attract pilgrims by the thousand, seeking hope and health where other avenues have failed. During the latter part of the twentieth century, the developed countries of Europe and North America saw a massive influx of 'health tourists' from the oil-rich countries of the Middle East, seeking high-quality care that was unobtainable in their own countries. Several Middle Eastern governments have established 'health offices' in cities such as London and Washington, DC, for the purpose of facilitating such care, often seen as an extension of the countries' own health service arrangements. Today, there is an established, bi-directional flow of health tourists between developed and developing countries.

Health tourism today

There has been recent, rapid growth in health tourism from developed to developing countries. This has been especially marked in regions such as Southeast Asia. More than 1.28

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million foreigners underwent treatment in Thai hospitals in 2005. In Malaysia, 300,000 foreign patients were treated in 2006, a figure that is growing at an annual rate of 30%. In 2006, 410,000 foreigners visited Singapore to obtain healthcare. India is also a popular destination, accounting for half the value of an industry that now has a turnover in Asia alone that will be worth $4 billion by 2012. Half a million US citizens travelled abroad to receive medical care in 2007, and 1.29 million UK citizens travelled abroad for dental treatment.

Drivers

Economics is by far the most powerful driver for this recent trend (Table 31.1). The combination of long waiting times for access to publicly funded care (where available at all), and the high cost of medical insurance, or of uninsured care in the private sector, leads many people suffering from non-acute medical conditions to examine the options for treatment elsewhere.

Economic drivers apply equally to non-surgical, 'one-off' treatments that include residential addiction rehabilitation programmes, with savings of up to 75%. Resource availability may be another key factor: ready access to good facilities may simply be unavailable locally, at any price. Another key driver may be legal or social issues, for example in the case of women seeking termination of pregnancy or fertility treatment outside locally acceptable social criteria (such as maternal age), or in people seeking assisted suicide. Such drivers may act in combination: besides being legal and accessible, gender reassignment surgery in Thailand may be ten times cheaper than in the west, or the Middle East, with 'good results' [3].

Table 31.1 Surgery in USA and Asia (costs in USD)

	US	India	Thailand	Singapore
Cardiac bypass	80–130K	6.7–9.3K	11K	16.5K
Cardiac valve replacement	160K	9K	10K	12.5K
Angioplasty	57K	5–7K	13K	11.2K
Hip replacement	43K	5.8–7.1K	12K	9.2K
Hysterectomy	20K	2.3–6K	4.5K	6K
Knee replacement	40K	6.2–8.5K	10K	11.1K

Source: Muddle GR (2008) Medical Tourism [2].

Benefits and pitfalls

The notion of low-cost healthcare, in an exotic and alluring environment, with the added prospect of being able to enjoy a leisurely recuperation far from the routine stresses of one's home surroundings is an attractive prospect. Unfortunately, for many people, the reality proves to be different. Many prospective patients place insufficient value on such factors as the professional indemnity cover of the doctors looking after them, the importance of follow-up care in the long term, and of easy access to a doctor who can take full responsibility for any problems that may crop up. One commentator describes continuing care as the Achilles heel of medical tourism. Procedures are seldom as simple as they may seem, and the economic advantages may quickly be destroyed by the need to travel long distances repeatedly, for management of complications.

In developed countries, medical, nursing and supporting staff, as well as hospitals themselves, operate within a strict regulatory and compliance framework, and have to meet exacting standards at every level. This carries clear benefits for patient protection that may be utterly invisible to the end user, but comes at a high cost. Language and cultural differences are also important, for example in pain management, and end-of-life decision making. There is a strong argument for obtaining care in one's own familiar environment, from a medical team with whom one can have a continuing, long-term relationship.

Role of the travel medicine specialist

Prospective health tourists may seek health advice from specialists in travel medicine, typically before travelling, though possibly while still away, or on return home. Specific health needs to consider include the following:

- risk assessment for travel-related health risks
- pre-travel immunisation
- malaria protection
- assuring a supply of routine medication if this has not been provided elsewhere
- where surgery is contemplated, it should certainly include protection against hepatitis B. Advice may also need to be offered in relation to preventing deep vein thrombosis during the journey home.
- the opportunity to counsel the traveller about the wisdom or otherwise of undertaking the intended treatment, and alerting them to any risks that have not been adequately considered.

A fuller analysis of pre-travel risk assessment can be found in Chapter 4.

Future trends

Future trends in health tourism are hard to predict – especially with the altered economic environment that has followed the economic downturn affecting many countries.

It is possible that private healthcare costs in wealthier countries may be driven downwards, reducing the cost differential between care at home and abroad. Reduced disposable income might reduce the ability of individual health tourists to travel at all, or conversely, might increase pressure to seek care abroad if care at home becomes further out of reach.

ETHICAL PERSPECTIVES

The most virtuous are those who content themselves with being virtuous without seeking to appear so.

Plato

Introduction

Travel solely or partly for the purpose of healthcare is increasingly common with both patients and healthcare professionals crossing geographical borders with increasing frequency. What implications does such travel have on ethical practice? Do morality and notions of 'ethical practice' remain constant irrespective of location? What particular ethical challenges arise for those working in the field of travel medicine? This chapter explores the ethical landscape of travel medicine and discusses the dilemmas that professionals working in the specialty may encounter. The aim is to discuss what the 'good specialist in travel medicine' would be like and to demonstrate how focusing on being 'a good practitioner' enables moral constancy no matter what specific ethical challenges arise for individuals.

Why might health tourism be perceived as a moral problem? After all, it has a long history. For example, in the UK, royalty regularly travelled to take the spa waters. Its significance perhaps lies in its purpose, namely that people are travelling not just to improve health by doing specific activities or going to a restorative destination, but specifically to seek medical treatment. The breadth of what is covered by the overarching terms 'travel medicine' and 'health tourism' is enormous. It is a field characterised by economic, social, political and cultural differences: the professional providing basic care to the most disadvantaged in the world and the affluent individual flexing the muscle of privilege on a quest for elective cosmetic surgery co-exist. Such diversity makes the ethical terrain unpredictable, vast and constantly changing. The moral questions relevant to aid work in a war zone appear utterly removed from those relevant to the provision of privately funded dental treatment. How can ethical analysis acknowledge such plurality yet remain useful to the millions of patients and clinicians participating in the rich realities of travel medicine on a daily basis? The answer might be to shift the focus from specific ethical problems and to seek common virtues or best practice to which all those working in travel medicine would aspire. Identifying considerations that, if not universal, warrant attention and thought whatever the context and provide a framework within which plurality of practice and contrasting experience can be effectively scrutinised. By exploring the fundamentals that both the poorest and the most advantaged value in clinicians, a model emerges that fosters an ethical framework that travels across borders and serves the widest range of patients.

The good doctor: virtues, health tourism and travel medicine

Travel medicine and health tourism raise questions about fundamental ethical concepts such as notions of justice, equity and fairness irrespective of the specific context in which care is sought and provided. However, due to the widely varying locations in which health tourism and travel medicine takes place, notions such as fairness can seem alarmingly elusive and vague as each subjective reinterpretation is adapted to differing cultural contexts and pragmatic constraints. Among those who study tourism (in its general rather than health-specific form), virtue ethics is of increasing interest [4]. It is suggested that it is also a valuable approach for those working within health tourism and practising travel medicine. Once the emphasis shifts to the individual and the motivations of those both seeking and providing care, what begins to emerge is a framework for ethical practice whatever the clinical scenario. So, what might a good practitioner in travel medicine look like? What are the characteristics that should inform best practice, whatever the setting? Writers disagree about what might appear on any list of virtues [5], but most accept that there is a core of virtues that are essential to ethical character and therefore practice. Table 31.2 suggests what a list of virtues for a professional working in travel medicine might incorporate and how practical wisdom may ensure the ethical enactment of these in clinical practice. It is not intended to be an exhaustive or definitive list but a starting point, and readers are encouraged to consider what they would include

Table 31.2 Virtues for a professional working in travel medicine

Characteristic or trait: the virtues in health tourism and travel medicine	Behaviour: the ethical enactment of virtue in travel medicine and health tourism
Trustworthiness	Those seeking care can rely on those providing it to be authentic, open and truthful even when there is difficult news to impart, e.g. about limited or absent resources and the systems for allocating those resources
Conscientiousness	A professional is competent and remains so throughout their career. In addition to competence, the clinician is reliable and accountable. They meet commitments and are alert to sustainability, e.g. where teams travel to regions of the world to provide immediate care that may not endure once the team leaves
Compassion	Even if there is no cure, there will be care and individuals are valued irrespective of perceived status, e.g. in situations where effective biomedical therapies are unavailable, there remains a case for providing care, advice and support
Sensitivity	Professionals are aware of the practice environment, competing agendas, power differentials, diverse interests and the importance of emotion. There is recognition that practice may be adapted according to circumstance. For example, in non-Western cultures, the dyadic model of patient–doctor confidentiality may be inappropriate when patients present as part of a family unit
Commitment to service	The role of the professional is to serve needs and to act in the patient's best interests. For some, this may extend to formal advocacy or activism, e.g. clinicians might use their experiences to highlight neglected issues in global health
Kindness	In all encounters, there is consideration and regard for others, e.g. irrespective of outcome, it is right to be generous, patient and responsive in clinical encounters
Humility	Practitioners are open to feedback, do not presume authority and acknowledge mistakes or misjudgements, e.g. partnership arrangements with local communities are meaningful and do not impose a particular or ethnocentric approach

in their own list of aspirations for best clinical practice in travel medicine.

Moral journeys: ethics in practice

Having suggested that virtues may be a useful way to conceptualise what it means to act 'ethically' as best clinical practice irrespective of context, the following section of this chapter demonstrates, via vignettes, how such an approach enhances ethical analysis of situations that occur at each stage of travel and health tourism.

Travel planning

Ethical practice in travel medicine begins before anyone has, in fact, travelled anywhere. A commitment to fostering a partnership in which information is shared honestly and individual needs are served while not losing sight of other interests requires clinicians to consider the ethico-legal responsibilities that arise prior to travel. In recognising what Crozier and Bayliss [6] term 'decision spaces', i.e. the context in which choices are made and the extent of those choices, the good practitioner is alert to the fundamentally moral opportunities available. Consider the vignette below.

> LH is a final year medical student who attends her university's occupational health department and asks to be immunised for her forthcoming elective in Uganda where she will be working in a remote hospital for 6 weeks.
>
> How might the practitioner who sees L make the most use of the ethical 'decision space' in which the consultation occurs?

At the most basic level, LH needs accurate, informed, reliable and appropriate advice that is communicated effectively. The virtues of competence, conscientiousness and commitment to service cover the range of behaviours from providing accurate information that is specific to the situation and meets the required standards of care. So far, so uncontroversial: it is the sort of encounter that occurs in clinics daily.

What else might a virtue approach to ethics prompt? The virtues of sensitivity, compassion and humility demand that the relationship, however fleeting, between LH and the clinician is not compromised by assumptions about what she knows, hopes and fears. Seeing the encounter through the lens of virtue ethics enhances the consultation. The acknowledgement that character and motive matter in ethical decision making results in a richer and more nuanced approach to even the most routine consultation. While there will be practical constraints such as time and workload, this potential 'decision space' is redolent with opportunity. What are the potential differences of which LH should be aware when living and working in Uganda? Is she particularly concerned about anything? Some readers may believe those questions to be the preserve of others, but a best clinical practice approach demands that a good practitioner identifies and responds not only to LH's explicit concerns and priorities, but also explores health in its widest sense to reach that which is implicit.

Beyond the walls of the occupational health clinic and the specific encounter with LH, there are wider moral questions to be asked about the role of medical students and global health. Students may provide additional manpower in challenging situations across the world, but they may also cause harm [7]. Students may choose a destination because of the experience that they anticipate having in a particular country where resources are scarce. Indeed, some students will exceed both their competence and role while on elective, creating significant ethical dilemmas for their peers [8]. Students, too, must be encouraged to reflect on the core virtues of best clinical practice that should not change however many geographical borders are crossed. Drawing once more on this approach, to prioritise 'experience' over human dignity and for the powerful to compromise the powerless is to act unethically: it is a failure of trust, compassion, sensitivity and kindness. Awareness of the standards expected of students, wherever they may be in the world, is as vital to clinical preparation for travel as vaccinating and providing sterile equipment [9]. Those already working in the field of travel medicine have an obligation to provide leadership and be role models to those who seek to follow in their professional footsteps.

In transit

The act of travel itself has potential for multiple ethico-legal dilemmas: medical repatriation, choices about when and why to cross geographical borders, coping with unfamiliar or absent equipment, and working with new colleagues are but some of the moral challenges that can arise. One particularly common (and dreaded) experience [10] is that of the mid-flight medical emergency described below.

> Dr AM, an ophthalmologist, is on a transatlantic flight. She has enjoyed lunch and three glasses of wine. Approximately 4 hours into the flight a call goes out asking for 'anyone who is a physician or nurse to make himself or herself known to a flight attendant'. Dr AM looks around and does not see anyone responding to the call. A second call is made asking for 'anyone medically qualified to make contact with a member of the cabin crew'. Somewhat hesitantly, Dr AM tells a flight attendant that she is a doctor, albeit 'a specialist in eyes'. The flight attendant leads Dr AM to the back of the plane where she finds a man in his late fifties. Dr AM observes that he is obese, sweating and has vomited. He is pale and clammy to the touch. One of the cabin crew has measured the man's blood pressure as 110/70. Dr AM begins to talk to the man, but the steward intervenes and says that the passenger does not speak any English. How should Dr AM proceed?

For many clinicians the fundamental question is whether there is a duty to act in emergency situations such as that described in the scenario above. It is a question that has both a legal and ethical dimension. Legally, the duty to intervene or 'rescue' varies depending on the jurisdiction in question and the relationship between the parties. For example, in the UK, there is no legal duty to intervene unless a fiduciary relationship exists, e.g. where a doctor has assumed responsibility for a patient. However, that is not the whole story because professional bodies commonly impose a normative requirement that a professional will act as a 'good Samaritan' and intervene to the extent that it is reasonable to expect given the circumstances and taking account of safety, competence and the availability of other options for care [11]. Such advice implies that there is, if not an obligation to act, a duty to weigh up the possibility of acting and assess the situation, and most defence organisations now cover (within certain parameters) clinicians who act in emergencies.

What might a virtue ethics approach add to Dr AM's dilemma? Trustworthiness and conscientiousness require Dr AM to explain the extent of her competence: she is an ophthalmologist and she has had a few glasses of wine. However, merely declaring a situation to be beyond her specialist knowledge is, taking a virtue ethics approach, not the optimal way to respond. Even if Dr AM feels that she can offer only limited assistance, the virtues of sensitivity, compassion, humility and kindness may require more from her. Dr AM can provide support to the crew and the sick man himself, which may take the form of keeping an eye on him, devising

non-verbal ways of communicating, suggesting that a call is put out for anyone who might be able to interpret or simply holding the man's hand and providing some comfort. These suggestions about the ways in which Dr AM might still support the passenger despite her specialism and enjoyment of a good lunch may seem unduly saintly or even mundane to some readers. However, ambivalence about, or antipathy towards, providing such basic care outwith the familiar structures of clinical work are themselves revealing. A virtue ethics analysis often throws the essence of healthcare and what it means to be a clinician into sharp relief. And, in so doing, other, less appealing human traits such as pride, ambition and selfishness are revealed as the 'shadow side' of clinical work. Dr AM's dilemma is not just a question of how one responds to emergencies in travel. Rather, that short vignette about Dr AM asks that most fundamental of moral questions: what does it mean to be a 'good' clinician and to 'care' for another person? The reader's response to this scenario is a barometer of moral values that extends well beyond the realms of 'Good Samaritan' acts.

In a strange land

Many ethical dilemmas in travel medicine arise as a result of the location in which care is sought or provided. It is common to view moral problems in travel medicine at a systemic level: big issues such as resources, conflict and political power are invoked to explain why a particular situation is or is not ethically acceptable. While the macro-level variables that shape global health are essential to ethical reasoning, there is a risk that these 'big' concepts become meaninglessly overarching and exclude the human factor in travel medicine and health tourism. Even the most bureaucratic and centrally administered system of providing, limiting or withholding healthcare is ultimately operated by people: clinicians, patients and representatives of other agencies are the heart of travel medicine. And people are individuals not commodities [12]. A virtue ethics approach demands that the individual reflect on how they work within a system. It is a moral framework that requires more than a resigned shrug or an exasperated rant about the latest obstacle in delivering healthcare.

As an example, let's consider the notion of 'cost', which is frequently cited as a reason for healthcare being sought or provided in a particular way or specific geographical location. For such analysis to be meaningful, 'cost' must be broadly interpreted and extend well beyond the merely economic. Individual clinicians who adopt even some of the virtues discussed in this chapter will quickly learn that there are multiple ways in which 'cost' both does and should inform healthcare, many of which are not objectively measurable, systemically controlled or universally experienced. Consider the scenario below.

> JH is a 40-year-old woman who has multiple sclerosis. She has become increasingly unwell in the last year and she uses a wheelchair. JH has decided to travel from her home in Scotland to Singapore, where she is intending to pay for private stem cell treatment. JH tells her neurologist about her plans. The neurologist is concerned and explains to JH that the treatment remains experimental and unlicensed in the UK. JH replies that she 'has done her homework'.

In purely economic terms it is relatively easy to assess the (considerable) cost of JH's proposed trip abroad for stem cell treatment. Yet, there are many other potential 'costs' to be considered in the ethical analysis of this scenario, some of which are shown in Table 31.3.

By taking an ethically based approach to the consultation, the broader and more nuanced aspects of 'cost' are revealed. The clinician who is open, trustworthy, conscientious and kind is the clinician to whom JH is most likely to reveal herself. A principle-based approach may prompt the professional to think about what autonomy, beneficence, non-maleficence and justice mean in JH's case, but it would be possible to do so without reaching the essence of the problem.

Table 31.3 Potential 'costs' to be considered

Individual cost to JH	Therapeutic cost to JH and the clinical team	Societal and political cost
Response to the trip and the treatment	Responsibility to inform JH	Division between those who can afford cutting-edge treatment and those who cannot [13]
Risks of the treatment and potential harm	Possible duty to prevent JH from travelling	Effect on local healthcare provision
Availability of ongoing care	Impact of proposed treatment and expertise to meet JH's needs following treatment	Impact on the reputation of the relatively 'young' science of stem cell research and its clinical application
Compromised trust in healthcare professionals	Effect of disagreement on therapeutic relationship and alliance	Commodification of human life and stem cells

For example, it might be argued that JH has made an autonomous decision and her neurologist has a responsibility to explain the risks of her choice, those risks in relation to her best interests and the wider issues of accessing care across borders. Yet such an analysis risks setting JH's preferences against those of the healthcare professional, thereby frustrating each party and creating an ethical stand-off. An ethical approach that prioritises trust, humility, conscientiousness and kindness provides a potential ethical bridge across the biomedical divide. The aim is not to 'be right' but to value characteristics and behaviours that have intrinsic value in all clinical encounters. JH and her neurologist may never agree about the wisdom of seeking stem cell treatment abroad, but they can prioritise their relationship and create a collaborative clinical environment in which the notion of 'cost' is understood to be multilayered, complex and differently experienced. Such an approach facilitates understanding and allows for change: a virtuous present creates the opportunity of a functioning future.

The example of JH and her neurologist describes a specific, micro-level situation, but what of the broader, macro-level dilemmas inherent in people travelling across the globe for healthcare? What is an appropriate ethical response to the inequities reflected and created by a system in which the wealthy travel [14] and the marginalised accept whatever is available, however questionable the quality? [12] Unfortunately, it is easier to identify the moral questions than it is to come up with effective solutions. Perhaps the best that can be offered is a multifactorial response encompassing a range of responses. Some of the possible approaches to the big questions in travel medicine and health tourism are shown in Table 31.4.

The extent to which individuals feel inclined, or able, to address the sometimes overwhelming moral complexity of health tourism and travel medicine will vary, but every single practitioner makes a difference to the experience of their patients on a daily basis. Reviewing those individual experiences, reflecting on the emergent themes and sharing expertise will inevitably contribute to, and enhance, the ethical identity of the specialty and its collective response to the moral dilemmas that feel so daunting when faced alone.

There's no place like home

The final stage of the moral journey is when the patient returns home after receiving care abroad. Of course, for some patients there are no sequelae of the care they obtained abroad and there will be a need for no, or negligible, follow-up when they return home. However, what is the situation when patients require significant follow-up as a result of care they obtained overseas?[15] A typical scenario is described below.

Table 31.4 Approaches to the big questions in travel medicine and health tourism

- Make visible the invisible: the first step in addressing a moral problem is to name it. All those who work in the field should be aware of, and highlight, inequity
- Identify the agents of change: who are the organisations and people who have the power to address injustice in healthcare provision?
- Map the moral landscape: what are the criteria that distinguish 'ethical' from 'unethical' practice in travel medicine and health tourism?
- Foster awareness of, and debate about, the sociopolitical effects on ethical practice and standards: what are the implications of a market-driven approach to the quality of care?
- Develop good practitioners who value, expect and demonstrate desirable traits and behaviours: systems are established and implemented by individuals
- Consider the role of the law and regulation in protecting and promoting cross-border standards of care irrespective of the healthcare system

PH has recently returned from Bulgaria, where she had liposuction. She presents at her local hospital's Accident & Emergency department with a fever complaining of feeling 'dreadful'. She has pain in her chest, feels breathless and is very frightened.

How should the good practitioner respond? There may be, indeed there probably are, multiple ways in which to respond and those different responses reflect the range of ways in which the ethical question or dilemma is perceived. What's more, different ethical problems and the concomitant range of responses can co-exist. PH needs care. The clinicians to whom she has presented have a duty to provide that care without judgement. The good healthcare professional will respond to PH with sensitivity, compassion and kindness. However, what of the wider implications? If PH is found, as seems likely, to have suffered the ill effects of a procedure that has been performed elsewhere and perhaps in a sub-standard way, what else should be considered? Again, clinicians will hold contrasting views about the extent to which they should engage with the wider ethical considerations arising from PH's example. For some, the primary and perhaps even sole responsibility is to provide care to PH. However, others will suggest that those with a voice and in a relatively privileged position in society should expose unacceptable practice and protect others from its effects. Activities such as lobbying, contributing to public health campaigns, contributing to debates, writing opinion pieces

and participating in information initiatives all have their moral antecedents in the notion of caring about inequities that exist beyond one's immediate remit. Indeed, it seems likely that the good clinician, who values commitment to service, does consider the wider context in which they work and is able to operate on multiple levels both to care for the patient in the room and influence the evolution of global healthcare.

Conclusion

Travel medicine and health tourism are fertile ground for ethical analysis. For ethicists, that may be welcome news, but for those working in the field as practitioners it can be overwhelming, frustrating and burdensome. The premise of this chapter is that despite the range of experience and plurality of perspective within the specialty, there are moral roots that ground the discipline and its practice. One way of understanding those roots is to reflect on the virtues and their practical enactment to discover what it means to be a 'good' clinician practising travel medicine. By reflecting on what it means to be a healthcare professional serving others, ethical practice becomes clearer and more authentic. Individual judgement, personal discretion and variety are to be embraced and not feared. Difference of approach can and will follow, but the core virtues are common. Social, political, economic and clinical challenges in travel medicine will remain a feature of the specialty, but every reader who strives to be a 'good' clinician can contribute to meeting those challenges.

References

1. Ford JMT (1986) Taking the waters at Tunbridge Wells. *Stress Med* **2**(2): 169–174.
2. Yap J *et al.* (2008) Medical Tourism: The Asian Chapter. Deloitte Consulting SEA.
3. Woodman J (2008) *Patients Beyond Borders: Everybody's Guide to Affordable, World-Class Medical Care Abroad*. Joseph Woodman. Ig Publishing, Chapel Hill.
4. Jamal TB (2004) Virtue ethics and sustainable tourism pedagogy: phronesis, principles and practice. *J Sust Tourism* **12**(6): 530–545.
5. Gardiner P (2003) A virtue ethics approach to moral dilemmas in medicine. *J Med Ethics* **29**: 297–302.
6. Crozier GKD and Bayliss F (2010) The ethical physician encounters international medical travel. *J Med Ethics* **36**(5): 297–301.
7. Shah S and Wu T (2008) The medical students global health experience: professionalism and ethical implications. *J Med Ethics* **34**: 375–378.
8. Bowman D (2009) Students whose behaviour causes concern: ethical perspective. *Br Med J* **338**: a2882.
9. Banatvala N and Knowing DL (1998) When to say 'no' on the student elective. Students going on electives abroad need clinical guidelines. *Br Med J* **316**: 1404–1405.
10. Gendreau MA and DeJohn C (2002) Responding to medical events during commercial airline flights. *N Engl J Med* **346**: 1067–1073.
11. General Medical Council *Good Medical Practice*. GMC, London.
12. Gray HH and Poland SC (2008) Medical tourism: crossing borders to access health care. *Kennedy Inst Ethics J* **18**(2): 193–201.
13. Pennings G (2002) Reproductive tourism as moral pluralism in motion. *J Med Ethics* **26**: 337–341.
14. Connell J (2006) Medical tourism: sun, sea, sand and . . . surgery. *Tourism Manag* **27**: 1093–1100.
15. Jones JW and McCullough LB (2007) What to do when a patient's international medical care goes south. *J Vasc Surg* **46**: 1077–1079.

Chapter 32 Medico-legal issues in travel medicine

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Introduction

This chapter presents some of the legal issues that arise in the practice of medicine in a travel setting. Global travel has become increasingly accessible to the general population, including elders and persons with complex medical situations, such that many travel operators now offer medical care through nursing and physician staff. Many physicians, whether paid staff or on personal holiday, encounter illnesses or injuries within their own groups, or in randomly encountered travellers. It is advisable that trip operators and physicians have a firm understanding of medico-legal issues that can arise during travel.

Legal foundation

Many legal issues that arise in the context of travel medicine are fundamentally similar to those in any ordinary case of alleged or actual medical malpractice. The tort of medical malpractice is merely a special case of the law of negligence. A brief review of negligence and medical malpractice law is thus in order, to ensure malpractice in travel situations is properly understood.

Medical malpractice defined

The law of negligence, from which medical malpractice law derives, entitles an injured party to recover compensation when they have been subject to 'conduct which falls below the standard established by law for the protection of others against unreasonable risk of harm' [1]. As in a negligence lawsuit, the plaintiff in a medical malpractice lawsuit generally must prove four elements: duty, breach, causation and damages. Although the analysis differs in certain critical ways, the same four elements must be proved in a medical malpractice lawsuit.

Duty

Duty is established by proving the obligation of the defendant to another individual or group to act or refrain from acting in a particular manner. In an ordinary negligence case, the issue of duty may be hotly contested. The plaintiff must prove that some sort of relationship existed between himself and the defendant, giving rise to the defendant's obligation of due care against unreasonable harm. In a medical malpractice case, however, the question of duty reduces to determining whether a physician–patient relationship exists.

The physician–patient relationship is usually established by expressly stated mutual assent, often in writing before medical services are provided. Typically, the patient expresses an agreement to pay for services, but payment is not a legal requirement to establish the physician–patient relationship. Furthermore, where there is no expressed consent on the part of the patient, the law may impose 'implied' consent to the physician–patient relationship, as in the case of care provided to an unconscious individual in an emergency department [2]. In the context of travel medicine, the physician–patient relationship (and thus duty) is typically established in the usual way; that is, an injured or ill trip member seeks the care of a trip physician or a local physician, and the physician agrees to treat or treats the patient.

The converse of the duty owed by a physician to their patient is the absence of any duty in the absence of the relationship. In particular, it is well-settled law in the United States that there is no duty of a physician (or any other individual) to rescue an individual in need of medical care or assistance, except in certain exceptional circumstances [3].

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

For example, consider a wilderness hiker who comes upon an individual suffering from severe, or even life-threatening, injuries. The hiker, whether a physician or not, has no legal duty to render assistance – not even a sip of water if he does not care to assist the disadvantaged individual.

As an example, David Sharp succumbed to severe altitude sickness and hypothermia while on Mount Everest in May 2006. Sharp sat down by the side of trail, and as his condition worsened, multiple climbers trekked past him and made summit attempts. A few climbers offered Sharp supplemental oxygen, but by all accounts, he was left to die, and perished on the mountainside. Sharp's story elicited international outrage over the parade of climbers who apparently ignored his plight. Sir Edmund Hillary decried the tragedy. 'I think the whole attitude towards climbing Mount Everest has become rather horrifying. The people just want to get to the top. It was wrong if there was a man suffering altitude problems and was huddled under a rock, just to lift your hat, say good morning and pass on by' [4]. It seemed that during this unfortunate episode, the philosophy of 'every man for himself' trumped any moral obligation to help a fellow climber in need. However, from a legal perspective, the climbers who ignored Sharp were perfectly within their rights. Sharp's case illustrates the rule that some special relationship must exist to create a duty, and conversely, that without that relationship, no duty exists. As discussed in the section Duty to rescue, there are many countries wherein the law does impose a duty to rescue.

In a travel context, a physician has a duty to the patients he or she agrees to treat, but not necessarily to everyone they happen upon during travels. For example, a designated cruise ship physician may have a contractual duty to the ship operator to be available to provide medical care to the passengers, but their mere presence on the ship does not establish a physician–patient relationship between them and every passenger. As in an ordinary medical malpractice case, only when the physician–patient relationship is established can a plaintiff prevail in proving medical malpractice in a travel setting.

Breach of duty

The issue of breach of duty reduces to the question of whether the physician's treatment was in accord with the standard of care. That is, did the physician exercise the degree of skill and care that would be expected of a reasonably competent physician in the same or similar circumstances? In medical malpractice cases, the issue of 'standard of care' is often argued with the use of expert witness testimony. In what may become a 'battle of the experts', the plaintiff's and defendant's experts will offer contradicting opinions about the standard of care.

The issue of breach of duty in a travel context is in theory no different to that in a normal medical setting. However, the analysis may substantially change because the standard of care is measured with reference to the circumstances. The diagnostic and treatment options available to a physician providing treatment may depend significantly on the setting and physical surroundings. On an aircraft or in the wilderness, physicians do not have the same resources available as in a hospital or physician's office. In a suit for malpractice, that physician's actions should be measured against what a reasonably competent physician, of the same professional standing, would have done under similar circumstances [5].

In a travel setting, the standard of care is much less likely to be well established than in a hospital. In a hospital, the standard of care for an open fracture may be to order X-rays, antibiotics and pain medication, and to obtain the opinion of an orthopaedic surgeon. By contrast, in a wilderness setting a physician may have only a rudimentary first aid kit and no assistant. Because the latter situation occurs rarely, establishing the standard of care becomes more of an academic exercise. Instead, experts theorise about what a reasonably competent physician would do under the circumstances. For physicians, insurance companies and attorneys, the decision in such a case may be much less predictable than that in a case where the standard of care is well established.

Causation

A physician who breaches duty of care can only be held liable for injuries that were the natural result of a continuous and unbroken chain of events caused by the breach. A full discussion of legal causation could fill several textbooks. For the purpose of this chapter, however, it is most important to understand the extent and limits to which injuries can properly be deemed to have been caused by a physician's negligence.

The most important factor in determining legal causation is foreseeability. That is, could a person of ordinary intelligence have foreseen that the same or a similar injury would have occurred as the result of the negligent act or of its omission? In general, the plaintiff can only recover a claim for injuries that were foreseeable [6]. Note that this is a much more restricted definition of causation than is the normal usage of the word, where an action can be considered a cause if it sets off a chain of events, foreseen or unforeseen, leading to the result.

In a travel context, consider the case of a physician who fails to follow the standard of care in treating a patient who suffers a laceration on an expedition, causing a lengthy hospitalisation that would not otherwise have been necessary.

Which of the following injuries would satisfy the issue of legal causation?

(**a**) The patient is transported by ambulance to the hospital, and suffers additional injuries when the ambulance crashes en route.
(**b**) The patient suffers decubitus ulcers during hospitalisation.
(**c**) During hospitalisation, a nurse mistakenly administers a drug to the patient that was intended for another patient, causing further injury.

In some sense, none of the injuries would have occurred if it had not been for the original physician's negligence. But only situation (b) satisfies the legal definition of causation with regard to the physician's negligence. Decubitus ulcers are an unfortunate but foreseeable potential consequence of a prolonged immobilisation. By contrast, neither an ambulance accident nor medication error is a foreseeable event related to the particular course of treatment. In particular, the lack of causation posed by (c) is an example of the rule that injuries resulting from the subsequent negligence of another are almost never imputed to the original defendant. Thus in a travel context, as in an ordinary medical malpractice case, a physician is liable only for injuries that foreseeably resulted from any departure from the standard of care.

Damages

The last element of a malpractice case is damages. An injured party can recover all economic losses accrued as the direct and proximate result of the injury, as well as for pain and suffering [1]. As a practical matter, this means that the patient can recover the full cost of treatment and recovery, as well as for foreseeable lost income. Notably, a plaintiff cannot recover for a 'lost chance', as for example, when the plaintiff misses a job interview because of a hospitalisation and consequently is not hired [7]. Like causation, the analysis of damages is generally no different in the travel context than in an ordinary medical malpractice case.

Duty to rescue and Good Samaritan Law

Duty to rescue

A physician who travels may be subject to liability in various jurisdictions, and the laws of those jurisdictions may vary significantly. One important difference may be the duty to rescue. In common law countries like the US, there is generally no duty to rescue, except in special circumstances, whereas in most civil law countries, like France, every individual has a duty to rescue a person in peril, provided the aid can be attempted without danger to the rescuer [8]. The contractual duty of a trip's physician to the trip's participants is precisely the sort of special circumstance that would give rise to a duty to rescue in the US. Operators, their physicians, and all of their employees should be aware of the existence or absence of a duty to rescue in the specific locations in which they travel.

In many countries where there exists a duty to rescue, the duty may be fully discharged by simply calling emergency services, whereas in other countries, aid must actually be attempted or rendered. Even in countries where there is no general duty to rescue, there are many exceptions. For example, all 50 states in the US have enacted 'hit and run' statutes that require drivers involved in automobile accidents to stop and render aid to injured parties. Further complicating the matter, Vermont and Rhode Island have enacted statutes imposing a general duty to rescue in the absence of risk to the rescuer; and Minnesota statute requires an individual to either attempt a rescue or to notify authorities [8].

Good Samaritan laws

Whether or not there exists a duty to rescue, almost all jurisdictions protect certain rescuers from liability for negligence with a class of statutes known as Good Samaritan laws. Good Samaritan laws are not likely to bar negligence claims against a trip physician who negligently treats a trip participant, because the absence of a pre-existing duty is generally a requirement of the statutes. These statutes are meant to protect individuals who happen on a person in need of rescue, not to protect physicians hired to accompany a trip for the purpose of providing medical assistance.

There are some circumstances in a travel context, however, where a medical professional may be able to claim Good Samaritan immunity against claims of negligence. An example is the 2008 case of McDaniel v. Keck. In that case, a school nurse paid to accompany a field trip, for the specific purpose of providing first aid to the trip's students, provided emergency medical care to a child who was not a field trip participant. The Supreme Court of New York held that the nurse was entitled to Good Samaritan immunity against negligence claims arising from the incident, because the nurse had no pre-existing duty to the injured child [9]. Under McDaniel, a physician may be able to defeat negligence claims for treatment of persons they randomly encounter during the course of the trip. However, a trip's physician or nurse will not be able to claim Good Samaritan immunity for treatment of the trip's participants.

Liability of the trip operator

This section addresses the issue of whether the trip operator shares liability for malpractice by a trip's physician. A trip

member who sues the trip's physician for medical malpractice has significant incentive to include the operator as a defendant. Juries tend to have less sympathy for corporations, and the corporation is usually considered a 'deep pocket' defendant, which can likely afford a greater judgement or settlement payment. However, operators usually hire trip physicians in the capacity of independent contractors, rather than as employees. This leaves uncertainty as to whether the physician is acting as an agent of the operator, in which case the operator may share liability for malpractice, or independently, in which case only the physician would be liable for his actions.

Generally

In the US, much of the law of trip operator liability has been litigated between cruise ship operators and their passengers. A series of cases over the past century has established a majority rule that a trip operator is not liable for the negligence of a physician hired as an independent contractor. A minority of courts has held that in certain limited circumstances, the operator may be liable for the negligence of its trips' physicians.

Majority rule: Barbetta For more than a century, the general rule has been that a tour operator that brings a physician on board a ship for the benefit of its passengers is not liable for the physician's negligence. In 1988, the Fifth Circuit Court of Appeals handed down a ruling in the case Barbetta v. S/S Bermuda Star that explicitly absolves the operator from liability for the negligence of a physician, stating the following rule.

> When a carrier undertakes to employ a physician aboard ship for its passengers' convenience, the carrier has a duty to employ a physician who is competent and duly qualified. If the carrier breaches its duty, it is responsible for its own negligence. If the physician is negligent in treating a patient, however, that negligence will not be imputed to the carrier [10].

The Barbetta court offered two main justifications for its ruling. First, the tour operator does not have the capacity to control the relationship between physician and passenger. Second, since the trip operator is not in the business of providing medical services, it lacks the requisite expertise to supervise a physician who is on board as a convenience to passengers. The court reasoned that the deficiency in control and expertise would leave the trip operator in a most unfair position were it subjected to liability for its physicians' negligence. Both before and after Barbetta, courts have consistently followed what has clearly become the majority rule. It has thus been commonplace for judges to dismiss on summary judgement (without conducting a trial) complaints against a carrier that are predicated solely on the negligence of a hired physician [11–14].

Minority rule: Nietes A minority of courts have followed a rule set forth in 1959 in the case Nietes v. American President Lines, Ltd. The Nietes court was aware of the justifications for the majority rule later followed by Barbetta, but dismissed them as non-dispositive. After all, a shipping company's employed captain has control over the navigation of the ship. If a passenger is injured because of the captain's negligence (e.g. the ship runs aground while the captain is drinking alcohol at the helm), the trip operator shares legal liability regardless of whether or not any corporate officer has expertise in the realm of navigation. [15] So, by the Nietes court's reasoning, the lack of circumstantial control over the physician and their medical expertise should not be a bar to liability. Instead, just as the company would be liable for its crew's negligence, it should be liable for the negligence of its medical staff.

Recent trends The rule of Nietes has seen a recent resurgence, and although Barbetta is still commonly referred to as the majority rule and Nietes the minority, recent cases have split between operator immunity. Some courts have continued to follow Barbetta and barred cases from proceeding against the involved shipping company if the case is based on its physician's negligence. [13] Others have followed Nietes and allowed these cases to proceed [16, 17].

An example of the uncertainty regarding operator immunity is the case of Carlisle v. Carnival Corp [11, 18]. A Florida Circuit Court followed the majority rule and dismissed the plaintiff's suit against Carnival. The District Court of Appeals, however, followed Nietes, and reversed the dismissal. Finally, however, the Supreme Court of Florida reversed yet again, ruling that for the sake of consistency, Barbetta should be followed whenever possible.

Although it was subsequently reversed, the appeals court's opinion in Carlisle was notable because it went beyond the control and expertise arguments of Nietes and argued that economic considerations support operator liability. Tour operators benefit substantially from having a physician onboard. Not only is the cruise more attractive to cautious or medically complex passengers, but operators avoid the substantial duties and concomitant expenses that might attend a health emergency during the cruise. An operator has no legal duty to provide a physician, and is perfectly within its rights to sail without one [19, 20]. However, general common law duty of care for passengers might require the operator to dock the boat to allow a sick passenger to disembark, thus incurring substantial port fees and other costs, as well as potential liability to other inconvenienced passengers. In the face of these potential costs, cruise operators usually prefer

to have a physician on board; the Carlisle court suggested that the reality of the arrangement is that the physician is present just as much for the convenience of the operator as its passengers. In this manner, the minority rule dismisses the suggestion that since medical services are not central to the operator's business, it should avoid liability. Instead, since the operator benefits substantially from the relationship, according to the minority rule, its liability would be considerable.

Barbetta, Nietes and Carlisle leave a good deal of uncertainty in the realm of operator liability. Courts have ample justification and precedent to support liability under Nietes or immunity under Barbetta. Prudent operators, though they may vigorously defend their immunity if sued, will thus operate under the assumption that they may be liable for the negligence of their trips' physicians, and take reasonable steps to avoid such negligence.

Negligent hiring

Although there remains uncertainty as to whether an operator may be liable for the negligence of an independent contractor physician, there is no uncertainty whatsoever with regard to an operator's duty of care in hiring a suitable physician. A trip operator must take reasonable care to hire physicians and medical staff who are duly qualified and experienced to handle the responsibilities of the position for which they are hired. If they do not, the operator may be liable for harm resulting from its medical staff's negligence under the theory of negligent hiring.

The 2002 case of Jackson v. Carnival Cruise Lines, Inc. is indicative of screening on the part of an operator sufficient to bar liability under a theory of negligent hiring. In that case, a Florida District court granted summary judgement dismissal of the plaintiff's claims of negligent hiring on the basis that the defendant cruise line both had proper procedures in place to ensure hiring of duly qualified medical staff and had followed those procedures in hiring the physician and nurse against whom negligence was alleged. Among the circumstances considered relevant by the court were that Carnival employs a director of medical operations who ensures that physicians and nurses are properly investigated and qualified for their positions, and medical staff members are required to acknowledge in writing that they have received and reviewed all policies and training documents. Furthermore, the court acknowledged that the physician in the case had 'excellent qualifications' for the position of ship's physician, including medical licences in South Africa, the UK and Australia; certification in advanced cardiac life support (ACLS); and 11 years of general practice in anaesthesia, surgery, and obstetrics and gynaecology. The nurse had a long service history aboard cruise ships, positive recommendations from several former employers and certifications in basic life support and ACLS. Thus, the court concluded, whether or not the physician and nurse were negligent, Carnival had discharged its duty to hire suitable medical staff [21].

The lessons from Jackson for tour operators are threefold. First, operators should maintain policies and procedures to screen candidates for medical positions. Second, operators should document all aspects of their compliance with these policies, qualification of individual medical staff and communication with medical staff regarding expectations as to the level of expertise required for the job. Third, and perhaps most important, operators are best protected by hiring physicians with background and experience that are well matched to the medical situations that are likely to arise in the particular circumstances of travel. To judges and juries, possession of appropriate certifications is likely to be a substantial factor in confirming that a physician is duly qualified.

Limited duty to transport

Operators have only minimal duties to transport a participant to a medical facility. In May 2009, for example, a Florida District court dismissed a suit against Carnival Cruise Lines in which the plaintiff sought damages for Carnival's failure to adequately arrange for transfer of the plaintiff to a hospital in Panama after the plaintiff suffered a stroke in a Panamanian port. The court reasoned that Carnival had no duty to provide medical transportation services, following the Barbetta rule that a shipping company is not in the business of providing medical services to passengers [22]. This is not to say, however, that an operator has no duty whatsoever to provide medical transportation. However, their duties are likely discharged as soon as the operator has taken reasonable care to transport the participant to a place where there is access to emergency services. As a practical matter, operators should have procedures in place to evacuate participants to within reach of emergency services, as well as contact information for emergency services for the areas in which they operate.

Reducing exposure prior to travel

This section discusses several critical steps that trip operators and physicians can take to reduce potential medico-legal exposure before situations arise:

- warning trip participants of risks inherent to travel
- screening and clearing participants prior to travel
- disclaiming liability through participation agreements
- maintaining adequate insurance coverage.

Duty to warn

Trip operators have no legal obligation to warn participants of hazards that are equally obvious to both participants and operators [23]. Conversely an operator would have to warn of risks of which they are aware or should be aware that are not obvious to the participant [23]. Obvious hazards include, for example, motion sickness on a boat or cold temperature on a ski trip. Non-obvious hazards include, for example, the risks of flying too soon after scuba diving or the incidence of malaria at a destination. With regard to medical care, an operator has no duty to warn of potentially substandard medical care in the destination country [24].

Medical clearance of participants

Obtaining screening information enables a trip operator to better fulfill the duty to warn participants. Many lawsuits have resulted from accidents that relate to interaction between the travelling conditions and an undisclosed pre-existing health condition. Participants of US origin should be informed that health information is protected by the Health Insurance Portability and Accountability Act (HIPAA) and the mere existence of a health condition does not necessarily preclude participation.

As discussed below, this process is a sword that may cut both ways, in that it can reduce the occurrence of health issues on the trip, but also expose the operator to accusations of discrimination and further negligence in failing to adequately warn based on the information obtained through the screening process. When health information is obtained in the US for medical clearance purposes, compliance with HIPAA is paramount. All information must be secured and only accessible to those who need to know [25].

Although there is controversy over the legal right of travel agencies and outdoor operators to obtain health information, simple medical screening is widely accepted as a way to reduce the likelihood of illness or injury for a trip participant, given the potential environmental hazards and conditions encountered by participants. A trip operator's knowledge of pre-existing medical conditions can help guide the selection of useful pre-trip medical information for a particular participant. A participant may not realise how a health condition, albeit well controlled at home, can be stressed with a change in sleep schedule, high altitude or other environmental factor(s) that exists in a foreign setting or during certain activities. For example, some life jackets have flashing (strobe) lights, which activate when immersed in water. Since these lights have potential to induce seizures, persons with seizure disorders should be warned about such equipment, and operators reviewing information about a participant with a seizure disorder should equip the trip with alternative life vests. Scrutinising the travel itinerary and equipment for hazards greatly lowers the chance of harm and subsequent liability.

It should be noted that if an operator requests medical information from participants, there may likely exist a reasonable expectation on the part of the participant that the operator has reviewed the information. Failure to adequately evaluate the information could render the operator and reviewing physicians subject to further liability under the law of duty to warn. In certain circumstances, the trip operator may be in a better position than the participant to predict how a particular health condition might be influenced by the travel environment, schedule and equipment. Physicians aware of a pre-existing medical condition should thus educate the participant about potential hazards and adjust the trip itinerary as needed.

Some participants may be reluctant to provide complete or accurate information regarding their medical conditions for fear that they will be denied participation. To the extent that it is possible, operators should attempt to elicit honest responses by conveying to participants that the information will be used for their own benefit. Barring participation is an option that the operator can consider, but as the next section describes, there are potential legal exposures that accompany this decision, so it should be undertaken with due care and consideration.

The Americans with Disabilities Act

A US operator who either modifies a trip or bars a participant because of the participant's health conditions should do so in accord with The Americans with Disabilities Act (ADA). The ADA was enacted to guard against discrimination of persons with disabilities, and includes a prohibition against barring a participant with a disability 'unless such criteria can be shown to be necessary for the provision of the good, services, facilities, advantages, or accommodations' [26].

Certain circumstances and health conditions, however, pose real and significant dangers to participants. Denying access to a trip, if medically necessary, must be accomplished carefully, utilising full compliance with the ADA. Even when the operator's screening is in compliance with the law, an ADA challenge is not uncommon, so physicians and operators should be aware of this liability and familiar with all components of this law.

In travel medicine, the primary consideration is always the participant's safety. An operator or physician is not obligated to allow participation in activities that pose a threat to health or safety of the participant or others. However, the operator is required to make accommodations and adjustments, at the operator's expense, to reasonably eliminate any threat to

safety. For example, cruise ships must have handicapped-accessible rooms. This accommodation obligation may go beyond simple adjustments, for example providing an assistant to a visually impaired trekker. The requirement to provide accommodations for a disabled traveller only lapses when the accommodation fundamentally alters the nature of the trip. Consequently, to refuse access to a trip, the operator must show that participation poses a threat to health or safety, and/or that adjustments to the trip would fundamentally alter the nature of the trip [27].

Participation agreement

Whether or not an operator screens participants, it may be able to reduce its liability with a participation agreement that includes a disclaimer of liability. A disclaimer of liability may absolve the operator from liability in certain circumstances; but in many other circumstances, courts will set aside disclaimers that are overly broad or otherwise unfair to the participants.

Details of the potential risks should be defined, including environmental hazards, recommended immunisations, political situations in the countries of travel, lack of access to sanitation and the type of available local medical care. Participants must receive the agreement far in advance of the trip. Presenting the indemnity agreement at the start of travel places undue pressure on the participant given the time constraints and expenses already incurred [28]. Courts will likely not enforce an agreement signed under those conditions; furthermore, courts will not enforce a release of gross negligence. A transparent and clear participation agreement may reduce liability for foreseeable risks inherent to the nature of the travel and activities when presented to the participant in a timely manner.

Insurance

In a litigious era, it is essential for operators and physicians to obtain and maintain adequate insurance coverage. No matter how complete the warnings, aggressive the participant screening, thorough the participation agreement and carefully a physician follows standards of care, poor outcomes are inevitable. It is thus critical that operators and physicians possess insurance that is both sufficient to cover potential damages and sufficiently broad to cover the geographical and medical scope of anticipated services. Since the physician is as or more likely than the operator to bear the costs of liability in a malpractice case, he must be absolutely sure to have insurance that covers his practice in the travel setting.

Before a physician embarks on the practice of medicine outside of their normal practice, they should contact their insurance provider to ascertain what, if any, trip activities are covered. In all too many cases, physicians are unknowingly practising outside the scope of their existing coverage and thereby exposing themselves to potentially devastating litigation. If specific roles of the physician are not covered contractually, the physician may request an addendum to the existing policy.

When defining coverage for travel medicine, the policy should not be limited to disputes arising under the laws of the jurisdiction of the operator's physical headquarters. Although trip operators will often attempt to obligate participants to contractually resolve disputes in a preferred jurisdiction, it is quite possible that the case will be heard in a foreign jurisdiction. Obtaining an insurance policy that is validly interpreted across jurisdictions is critical in the field of travel medicine.

Legal counsel should review any supplemental coverage. In general, the smaller the operator or more unusual the travel activity, the greater the difficulty in finding an affordable policy that adequately covers the risks. Larger travel operators may have the resources to include a physician under a larger 'umbrella' policy.

Practical considerations

Certifications

As already discussed, operators may be subject to liability for the negligence of their medical staff under the theory of negligent hiring. Operators are therefore best served by hiring physicians and nurses with training backgrounds appropriate to the circumstances most likely to be encountered. Board certification and professional experience are critical considerations, as are other forms of certification. For example, the following is a non-exhaustive list of entities offering certifications that may be appropriate to a variety of travel circumstances.

- International Society of Travel Medicine (ISTM): this organisation offers a Certificate in Travel Health, recognising individual excellence in knowledge in the field of travel medicine, associated with pre-travel care and consultation. The exam is open to all licensed travel medicine professionals, including physicians, nurses, pharmacists and others [29].
- International Medicine Fellowship: this fellowship entails education and experience of 1 or 2 years post-residency. Various academic hospitals in the US and other countries offer international fellowship programmes for physicians.
- Wilderness Medicine Fellowship: this fellowship entails education and experience of 1 or 2 years post-residency. Various academic hospitals in the US offer wilderness medicine fellowship programmes for physicians.

• Wilderness Medicine Training Center: these programmes offer a variety of certifications, ranging from Wilderness Emergency Medical Technician (EMT) Module, which requires EMT training prerequisite, to Wilderness First Responder (WFR) certificate to Wilderness Advanced First Aid certificate. These programmes generally have fewer prerequisites for participation [30].

Prescription medications

Common law generally requires prescription medications to be dispensed in a controlled manner. Prescriptions should be written to a specific person with known age, allergies and in consideration of intake of other drugs. This is not always the practice, however, in travel medicine. Instead, prescriptions are written to an operator or organisation and may be dispensed by non-physicians in the field. One notable drug, auto-injectable epinephrine (e.g. Epi-Pen), is an exception to the rule. For example, California and New York have laws permitting non-physicians, such as teachers and trip leaders, to carry epinephrine auto-injectors to be used at their discretion (after a short training course) [31]. Other prescription drugs frequently carried by trip leaders include antibiotics, bronchodilators and corticosteroids (inhalers), and pain medications. This practice has not been subject to litigation; hence there exists no legal precedent. Among the directors of organisations that permit prescription medications to be used by (non-medical professional) trip leaders, it is generally thought that the benefit of having these medications in remote locations outweighs the risk of harm and potential liability. This practice exposes the organisation and physician to considerable legal liability, because malpractice insurance does not cover any illegal practice. Physicians affiliated with a large organisation may obtain some protection under the organisation's umbrella policy.

Medical assistance during air travel

An estimated two billion people fly commercially each year and in-flight medical illnesses are a regular occurrence, with an average of between 13 to 30 incidents worldwide daily [32]. Fear of liability is cited as the chief source of most physicians' unwillingness to assist [33]. The Good Samaritan law was enacted specifically to address this concern and provide protection to those who choose to assist. A few caveats are worth mentioning pertaining to the Good Samaritan law and air travel.

The Good Samaritan law operates under the principle that physician action is voluntary. This principle holds true in the US, Canada and the UK. Recall that there is not international consensus on the physician's duty to assist. Australia and many European countries require by law that a physician assist in the event of a medical emergency. According to international law, the country where the airline is registered determines jurisdiction, which could be of significance given the disparity between countries of the obligatory versus voluntary nature of the physicians' actions. The country of citizenship of both the plaintiff and defendant potentially could also influence jurisdiction [34, 35]. Physicians should at least be familiar with the law regarding obligatory assistance for their country of citizenship.

Physicians in the US who assist in a medical emergency during air travel are protected by both the broader Good Samaritan law and the Aviation Medical Assistance Act of 1998. This act reinforces the Good Samaritan law and makes the specific exception that gifts in the form of travel vouchers, seat upgrades or amenities are not considered compensation [36].

To date, in the limited area of air travel, no litigation has been successful against a physician for providing in-flight care in the US. Physicians have been named in legal actions for rendering care for in-flight medical illnesses, but effectively protected by the Good Samaritan law [32]. Additionally, many airlines have a physician medical director on the ground whom the crew contacts in the event of an emergency. If no physician is present on the flight, the medical director guides medical care in-flight and has the responsibility for making the decision to redirect air travel or land emergently. If a land-bound medical director is part of the care team, the voluntary in-flight physician reduces liability by deferring landing or redirecting decisions to the director and focusing only on necessary stabilising interventions until definitive care is available on the ground.

Travel medicine clinics

Practising medicine outside of one's domestic borders may also entail extended stays in developing countries, either at established clinics and hospitals or with a mobile clinic team. This practice environment often necessitates difficult treatment decisions. Physicians have neither the luxury of numerous diagnostic tests and imaging modalities nor the opportunity to watch illness over time, so medical decisions must frequently be made with comparatively suboptimal testing and timing. Since physicians cannot monitor the patient with long-term follow-up, the patient's health issues must be addressed as completely as possible in a relatively short period of time. Any complication, always a risk in the best of circumstances, is magnified in the setting of limited follow-up.

Any physician considering practising medicine in such a setting should contact the legal department of the organisation with which they are working to determine what medico-legal issues physicians have encountered, the nature

of existing insurance coverage, and whether any supplemental coverage is recommended. Furthermore, the physician should familiarise themself with the destination country's domestic legal system, at the very least determine whether it is a common law or civil law system, and whether there are any peculiarities to its malpractice law. Although legal suits are extremely rare in these circumstances, knowledge of potential liability and malpractice insurance coverage ensure that the physician has protected themself to the extent possible.

Informed consent

Being in the wilderness or travelling to remote locations does not preclude the necessity for obtaining informed consent. In the most emergent situation when the patient lacks capacity, implied consent supplants informed consent [2]. Otherwise, as with in-hospital treatment or procedures, the risks, benefits and alternatives must be clearly discussed with the patient prior to intervention. A person in full capacity has the right to decline medical intervention. Violation of the right to decline medical care constitutes battery under many legal systems. Physicians obtaining consent should document the conversation or circumstance in which consent is obtained, and when possible obtain a signature from the patient. The environment and available resources may affect the media or formality with which informed consent is documented, but the requirement for informed consent remains.

Documentation

Proper documentation can be difficult to maintain in travel situations, but it is of paramount importance. Not only does documentation enable better care for the patient, but it can be crucial in cases that result in litigation. While the conditions may be challenging, any documentation is better than no documentation. As with any medical documentation, the notes should include date, time and patient name. Documentation of medical decision making and the influencing environment further support the physician's case in the event of litigation.

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References

1. Restatement (Second) of Torts (1965).
2. Hernandez v. U.S., 465 F.Supp. 1071 (D.Kan. 1979).
3. Yania v. Bigan, 397 Pa. 316, 155 A.2d 343 (1959).
4. McKinlay, T (2006) Wrong to let climber die, says Sir Edmund. *New Zealand Herald* 24 May.
5. Raffey v. Tonder, 36 Md. App. 633 (1977).
6. Ortiz v. Santa Rosa Medical Ctr., 702 S.W.2d 701 (Tex.App.1985).
7. Boody v. U.S., 706 F.Supp. 1458 (D.Kan.1989).
8. Hyman D (2006) Rescue Without Law: An Empirical Perspective on the Duty to Rescue, 84 Tex. L. Rev. 653 (2006).
9. McDaniel v. Keck, 53 A.D.3d 869, 861 N.Y.S.2d 516 (3d Dept. 2008).
10. Barbetta v. S/S Bermuda Star, 848 F.2d 1364 (5th Cir. 1988).
11. Carnival Corp. v. Carlisle, 953 So.2d 461 (Fla.2007).
12. Doonan v. Carnival Corp., 404 F.Supp.2d 1367 (S.D.Fla.2005).
13. Hesterley v. Royal Caribbean Cruises Ltd., 515 F.Supp.2d 1278 (S.D.Fla 2007).
14. Suter v. Carnival Corp., 2007 WL 4662144 (S.D.Fla.2007).
15. Nietes v. American President Lines, Ltd., 188 F.Supp. 219 (N.D.Cal.1959).
16. Huntley v. Carnival Corp., 307 F.Supp.2d 1372 (S.D.Fla.2004).
17. Mack v. Royal Caribbean Cruises, Ltd., 361 Ill.App.3d 856 (2005).
18. Carlisle v. Carnival Corp., 864 So.2d 1 (Fla. 3d DCA 2003).
19. Mascolo v. Costa Crociere, Sp.A., 726 F.Supp. 1285 (S.D.Fla.1989).
20. Walsh v. NCL (Bahamas) Ltd., 466 F.Supp.2d 1271 (S.D.Fla.2006).
21. Jackson v. Carnival Cruise Lines, Inc., 203 F.Supp.2d 1367 (S.D.Fla.2002).
22. Gliniecki v. Carnival Corp., 632 F.Supp.2d 1205 (S.D.Fla.2009).
23. Kalter v. Grand Circle Travel, 631 F.Supp.2d 1253 (C.D.Cal.2009).
24. DeRoche v. Commodore Cruise Line, Ltd., 31 Cal.App.4th 802 (1994).
25. Health Insurance Portability and Accountability Act of 1996, 42 USCA § 201 et seq. (2000).
26. Americans with Disabilities Act of 1990, 42 U.S.C.A. § 12101 (2009).
27. Larsen v. Carnival, 242 F.Supp.2d 1333 (S.D.Fla.2003).
28. Brown R (2009) Basic Risk Management Concepts for Outdoor Programs, http://www.brownburkelaw.com/articles-risk_management.html (accessed May 2012).
29. International Society of Travel Medicine, http://www.istm.org.
30. Wilderness Medicine Training Center, http://wildmedcenter.com (accessed 15 July 2012).
31. California Department of Education. Administration of epinephrine autoinjectors. Ann. Cal. Educ Code § 49414, http://www.cde.ca.gov/LS/he/hn/epiadmin.asp (accessed May 2012).
32. Gendreau MA and DeJohn C (2002) Responding to medical events during commercial airline flights. *N Engl J Med* **346**(14): 1067–1073.
33. Rayman RB (1998) Inflight medical kits. *Aviat Space Environ Med* **69**: 1007–1010.
34. Hedouin V *et al.* (1998) Medical responsibility and air transport. *Med Law* **17**: 503–506.
35. Newson-Smith MS (1997) Passenger doctors in civil airliners – obligations, duties and standards of care. *Aviat Space Environ Med* **68**: 1134–1138.
36. Aviation Medical Assistance Act of 1998, 49 U.S.C.A. § 44701 (2000).

Chapter 33 Travellers' safety and security

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Introduction

Most travellers visit their general practitioner or travel clinics with thoughts of vaccinations and prophylaxis against exotic tropical and travel-related diseases. The most common causes of serious morbidity and of mortality in travellers, however, relate to accidents, injury and pre-existing illness, especially cardiovascular disease in older travellers [1–6]. The risk of severe injury is thought to be greater for people when travelling abroad [7]. An understanding of the epidemiology of travel-related injuries and serious illnesses can help stimulate attempts to prevent adverse outcomes of foreign trips. Indeed, it has been claimed, 'injuries are not accidents'. [5] Experts have suggested that injuries are predictable events that are amenable to scientifically founded intervention strategies [5].

Despite an understanding of serious injury and illness-related interruptions in travel, however, untoward events continue to occur. These risks should be covered by travel insurance to protect the traveller, although it is not known what proportion of travel agents or airlines give advice routinely on travel insurance; however, many are likely to have commercial linkages to travel insurance companies. Travel insurance is the most important safety net for travellers in the event of misadventure, and travel health advisers should reinforce this advice.

In addition, preventive strategies are not always developed and implemented. 'Accidents' continue to happen. When faced with injury and serious illness, travellers should be armed with emergency treatment supplies, a working knowledge of first aid and adequate insurance coverage. They should know how to access appropriate care at their travel location, particularly through the emergency assistance service of their travel insurer. The indications for and logistics of evacuation should be understood.

This chapter reviews currently known data about the morbidity and mortality of travel-associated injury and serious illness. It then proffers recommendations concerning pre-travel health advice and contingency planning.

General epidemiology of travel-related illness and injury

Fortunately, few travellers die or sustain serious injury [8]; however, each death or serious injury represents a major concern for travel health advisers and tourism authorities alike. To maintain a country's reputation as a safe destination and to identify potential areas where overseas visitors may experience health and safely problems, it is important to monitor available statistics on illness and injury of travellers. Perhaps it can be best summed up by Eitzinger and Weiderman [9]:

> The fact that the implementation of proper safety measures is at least to the same extent trust increasing as the absence of such measures is distrust increasing reveals that a destination can only benefit from the implementation of proper safety measures. (p. 852)

By reviewing overall morbidity and mortality in foreign travellers, one gains a perspective on the importance of serious illness and injury and the occasional need for emergency assistance, such as aeromedical evacuation and repatriation. While infectious diseases, such as travellers' diarrhoea, are common among travellers, they only rarely cause serious long-term consequences. Injuries and cardiovascular events are much less frequent occurrences among travellers, but they account for the bulk of ongoing morbidity as well as for most travel-related fatalities.

Principles and Practice of Travel Medicine, Second Edition. Edited by Jane N. Zuckerman.

Various investigators have studied the incidences of different health problems in travellers. The incidences of health problems vary between subgroups of the travelling population and between various travel destinations. It is evident that time-limited health problems, especially diarrhoea, are common and that illnesses or events provoking a subsequent decreased work capacity or an overseas death are much less common.

Musculoskeletal problems, mainly resulting from accidents and injuries, made up nearly one-fifth of claims made by travellers in an Australian study of travel insurance claims [10]. This was similar to a recent Swiss travel insurance study, where accidents involving the extremities made up 15.3% and accidents involving the head made up 4.7% of claim reports [11]. Some illnesses and injuries would likely occur no matter where in the world one was. Illness, however, is more common among travellers than among those staying at home. In addition, death related to injury is more common in at least male travellers than in those who do not travel [12].

The risk for travel-associated injury may be changing over time. One report including 16,000 holiday travellers during an 18-month period showed that 5% were injured during their trip, twice the rate noted 5 years earlier [13].

Mortality and morbidity associated with travel

Table 33.1 summarises the studies and the data showing causes of travel-associated mortality. For age-related comparison, of 98 residents of Amsterdam aged 0–14 years who died abroad (most while visiting friends or relatives in either Turkey or Morocco), accidents (especially motor vehicle related), gastrointestinal infection and congenital anomaly were the most common causes of death [14]. In that study, fatal infections were most common in Morocco, and fatal accidents usually occurred during the first decade of life [14]. While the different studies employed varying methodologies that limit the comparative value of the data, it is clear that injuries account for much of overseas death, that most fatal injuries are motor vehicle related and that cardiovascular disease increases with the advancing age of the travelling population.

An Australian study showed that the crude mortality rate for short-term travellers and work party members abroad was only about 10/100,000/month or about 0.1% annually [3]. About 35% of deaths abroad were the result of ischaemic heart disease, with natural causes overall accounting for some 50% of deaths [3]. Trauma accounted for 25% of deaths of Australians abroad [3]. Injuries were the reported cause of 18% of all deaths, with the major group being motor vehicle accidents, accounting for 7% of all deaths, which appeared to be over-represented in developing countries [3]. A similar pattern of mortality was observed in Swiss [15], American [12, 16, 17] and Canadian [4, 18] travellers abroad. Deaths of Australian tourists overseas have also resulted from air crashes, drowning, boating accidents, skiing accidents, bombs and electrocution [3]. Homicides, suicides and executions combined accounted for about 8% of all deaths [3]. Most fatal incidents involving American and Swiss travellers were traffic or swimming accidents [15, 19]. Deaths of tourists visiting Australia was similarly found to be due mainly to motor vehicle accidents and accidental drowning [6]. Infectious disease was reported as the cause of death in only 2.4% of Australians travelling abroad [3]. Several Australian studies have also examined Australian hospital data and have found that motor vehicle accidents and water-related incidents are major causes of traveller injuries requiring hospitalisation [20, 21]. Highest injury risks have also been reported in New Zealand among some of the adventure sports, such as snow sports, bungee jumping and horse riding [22]. Adventurous pursuits of travellers are likely to increase the risk of fatal injury [23]. Falls, homicide and suicide are also reported. From these studies, it could be concluded that advice concerning accidents and injury avoidance was probably more practical than overemphasising protection against infectious diseases.

An Australian study found that this risk of dying abroad was probably similar to that at home, but the risk varied depending on the destination [3]. New Zealand and north-east Asian countries were among the safest countries to visit [3]. Similarly, accident fatality rates in men from the US were higher in developing countries than developed countries or at home [19, 24]. The most dangerous destinations for Australian tourists were Europe and Central and South America, with Southeast Asia accounting for deaths in proportion to the number of visitors [3].

Epidemiology of specific sorts of accidents and injuries

Transportation accidents

Motor vehicle crashes are the most common type of fatal injury-provoking situation reported by travellers, and collision-induced injuries are also common among travellers surviving their injury [25–27]. Motorbike accidents (MBA) account for approximately 79% of deaths and 73% of injuries on the roads in Thailand [28] and this could impact on travellers using motorbikes. In a study of helicopter emergency retrieval medical service (HEMS) missions in the UK, travellers were grossly over-represented among HEMS missions involving a pedestrian being struck by a vehicle with serious resulting trauma compared with the local population

Table 33.1 Summary of mortality studies of travellers

Country	Years	Source of population	Results	Reference
Inbound traveller studies				
Australia	1997–2000	Death Certificates reported to the Australian Bureau of Statistics	Natural causes, 76%, Accidents, 20%, Suicides, 2%, Homicides, 1%	33
Australia	2001–2003	Death Certificates reported to the Australian Bureau of Statistics	Natural causes, 73%, Accidents, 23%, Suicides, 3%, Homicide, 1%	34
Turkey	1998–2002	Forensic documents, including court and autopsies	Accidents, 45%, Natural causes, 32%, Homicide, 17% Suicide, 2%	16
Outbound traveller studies				
Australia	1992–1993	Consular reports of deaths abroad	Heart disease, 35% Accidents, 18% Infections, 2%	3
Canada	1995	Consular reports of deaths abroad	Natural causes, 62.1%, Accidents, 25%, Homicide, 8%, Suicide, 5%	4
Canada	1996–2004	Consular reports of deaths abroad	Natural causes, 74%, Accidents, 18%, Homicide, 4%, Suicide, 4%	18
Scotland	1973–1988	Consular reports of deaths abroad	Cardiovascular disease was the major cause Trauma was the next most common Injuries, 21%	48
US	1975, 1984	US State Department documents	Cardiovascular events, 49%, Injuries, 25%, Infectious disease, 1%	12
US	1975, 1984	US State Department documents	Injuries Chronic diseases Suicides Homicides (all greater than Infectious/Parasitic)	19
US	1998, 2000, 2002	US State Department documents	Injuries, 13%	16
US	2004–2006	US State Department website	Examined 2,361 injury deaths only Motor vehicle accidents, 33%	17

[29]. Other forms of transportation accidents do not figure prominently; however, there are a number of examples of water and air transportation accidents involving tourists in the literature. Ferry and tour boat accidents appear to be a particular problem for foreign travellers in Thailand [10].

Travellers are reported to be several times more likely than local drivers to have accidents [30–32]. Several risk factors for motor vehicle crash-related injuries have been identified. Interestingly, international travellers to Australia who were involved in crashes were less likely to have high-risk behaviours such as alcohol or speeding than were local residents involved in crashes [26]. On the contrary, however, alcohol use was a primary factor in road traffic accidents among foreign nationals visiting Greece, especially among those

originating from Eastern Europe [32]. Tourist crashes are also more likely to relate to driver disorientation (such as occurs with jet lag) and fatigue [26]. Specifically, vehicle accidents were more common in visitors from countries where driving was on the other side of the road compared with the destination [33, 34], and wrong-side driving was common in crash-related injury and death [26]. Side of the road/side of the car familiarity has previously been identified as a factor in serious overseas visitor road crashes resulting in injury and death, along with fatigue, not wearing a seatbelt, language and signage difficulties [26], and generally driving unfamiliar vehicles in unfamiliar environments [26]. Needless to say, travellers licensed in one country usually drive in another country, where there may be considerable difficulties in comprehending road signage and understanding differing road rules [35], without any further training. Accidents involving wild animals make up about 5.5% of motor vehicle accidents involving serious casualties in Australia [36]. Night-time travel was also found to be a significant risk factor [36].

Accidental drowning

Accidental drowning and water sports-related injuries usually rank second in frequency after transportation accidents. A study of surf drowning deaths by Morgan and colleagues [37] found that international tourists had an annual average crude surf beach drowning rate of 2.36 per 100,000 population, corrected for average number of days of travel in Australia, representing almost 25% of the drowning deaths reported. Mackie [38] notes that unfamiliar marine environments are a particular hazard for international tourists. In 2001–03, 53 tourists from at least 23 countries drowned in Australia (approximately 18 per year) [34], which is a higher rate than that for 1997–2000 (15.5 per year) [33]. In the study of inbound tourists to Australia [34], tourists from Japan, China and Germany seemed to be at greater risk, although the highest number of overseas tourist deaths due to drowning came from the UK. Understandably, many tourists travel to participate in activities that are not part of their usual routine. This provides novel experiences, but it also implies that the travellers are opening themselves to risks of activities with which they are incompletely experienced.

Water-related injuries have been linked to pre-existing medical conditions (epilepsy, cardiac disease and fatigue), inexperience, failure to follow a pre-established plan (for divers) and panic [26]. Alcohol and drug use play a role in some injuries, as does swimming alone; the male sex is also a risk factor [26, 27]. Two-thirds of tetraplegic spinal injury admissions have been linked to holidays abroad with a history of diving too steeply into shallow water [39]. Decompression illness was a common cause for admission in foreigners visiting Australia [40]. Drowning in pools accounted for most of the deaths of British children abroad [41].

Lacerations and fractures occur in travellers, and it seems that these injuries take place at a somewhat higher incidence among travellers than in the local population [25]. There is also evidence that injuries tend to be more serious in travellers than in local people [25].

Intentional injuries

Deaths due to homicides, suicides and poisonings are uncommon causes of deaths of travellers abroad. Indeed, as noted by Venditto and Mouzos [42] from their investigation of visitor deaths for the Australian Institute of Criminology: 'it can be said with reasonable conviction that the murder of overseas visitors in Australia is a statistically rare event' (p. 5). In that study, between 1994 and 2003, the murder rate of tourists was 0.9 per million short-term visitors to Australia. While deaths due to these events are rare, morbidity is relatively common, with about 25% of travel insurance claims being for loss, theft and muggings [43]. In 1999, six murders resulting from muggings in unlicensed airport taxis prompted a warning to be issued by the Australian Embassy in Bangkok on 6 June 1999 to all travellers arriving at Bangkok's International Airport [10].

Last, a drug culture exists in many tourist destinations. A recent study of young travellers visiting a Bulgarian nightlife resort identified several factors relating to personal safety, including violent security staff, overcrowding, shattered glass on surfaces, tolerance of dancing on furniture, and alcohol served to minors and overly drunken people [44]. A study of UK backpackers to Australia revealed that more than half had used at least one illicit drug when backpacking [45], although this rate tended not to greatly increase during travel, whereas alcohol consumption nearly doubled.

Detention of travellers

There are a considerable number of travellers detained in jails abroad. A major reason for incarceration of travellers abroad are drug charges, with about one-third of detentions in a Canadian study due to drug charges [46]. Interestingly, more than 50% of detailed females travellers were incarcerated on drug-related charges [46]. Most detailed Canadian travellers were jailed in the Americas, particularly the US [46]. Similarly, most Australians detailed abroad are in jails in the US, but also in other popular destinations for Australian travellers, including Asian countries such as China, Thailand, Vietnam and Indonesia (including Bali) [47].

Epidemiology of specific sorts of serious illness

Cardiovascular disease is a common cause of death and serious illness in travellers, especially those originating in industrialised nations [3, 4, 12, 18, 33, 34, 48]. This is most common in older travelers, and not all have had previous evidence of underlying cardiovascular compromise.

Malaria is the most common infectious cause of death in travellers [1], but it is still a small component of mortality of travellers abroad. There is a particular risk of malaria infection and death in travellers who are going to visit friends and relatives as compared with the typical tourist traveller [49]. Similarly, most returned travellers who had malaria in the US had not been on an appropriate chemoprophylactic regimen [49].

While human immunodeficiency virus (HIV) infection does not yet appear in statistical lists of fatal infections acquired during travel, there is a risk. It is thought that 10% of Swiss HIV infections are acquired abroad [1], and genetic studies of HIV suggest that European cases are increasingly of foreign origin [50].

Both culture shock and overt psychiatric illness can complicate international travel [51, 52]. Even visitors to Hawaii had an incidence of 220 psychiatric emergencies per 100,000 population [52]. It is difficult to compare these annual rates with a residential population in the same setting (1250/100,000), since the tourists usually did not stay for very long. Assuming that the average tourist stays about 2 weeks (4% of the year), this implies that the actual risk to travellers is much higher than in the baseline population. Clearly, travel often involves stresses such as family separation, distance from usual support systems, cultural and linguistic adjustment, jet lag, fatigue and illness. These stresses can provoke either new or relatively dormant psychiatric illness.

Pre-travel health and safety advice

There are no randomised clinical trials examining the prevention of accidents among travellers [53]. Travel health advisers need to review intended itineraries and activities with travellers as part of pre-travel risk assessment, discussed elsewhere [54], and include establishing the risks of the:

- destination
- mode of travel
- traveller's medical history
- intervention.

This assists travel health advisers in identifying risks and make informed recommendations concerning how to minimise these risks.

Personal safety

Personal safety is one of the most important areas for travel health professionals to cover when giving advice to travellers going to virtually any country. Individual responsibility is paramount, as it has been noted for some time that there are fewer people going on programmed package tours [55], with only about 43.6% of travelers to Thailand report being part of a group tour [10]. About half of general practitioners (GPs) in studies from New Zealand and Australia reported usually giving safety advice to travellers [56, 57], but GPs who saw a greater proportion of travellers were more likely to give safety advice [56]. Seventy per cent of travel health advisers in travel clinics usually advised travellers about personal safety [58]. A study of in-flight magazines in Australia revealed a paucity of advice concerning personal safety of travellers [59]. Travellers should also be advised about important safety nets, such as health and travel insurance and finding medical assistance abroad. Travellers are concerned about personal safety when travelling abroad. In a recent Australian study, travellers were more concerned about personal safety than terrorism and the prevailing emerging infectious disease threat of avian influenza [60, 61].

Muggings and assault

Muggings and assault are always potential hazards for travellers. It is important that travellers should use official taxi services at airports and train and bus stations and stay in reputable accommodation in safe areas, especially travellers who are not part of a group tour.

Muggings can happen to virtually anyone, anywhere. However, travellers, especially western travellers travelling in developing countries, may be considered rich by potential muggers, despite the realities of travellers' financial status [62]. Even tattered 'Nikes' can be a prize for muggers.

Travellers should avoid looking too much like tourists and wear understated dress. Travellers should try not to underdress, even in hot tropical locations, as this may transgress local culture and customs. Travellers should leave their expensive jewellery or watches at home in a safe place. They should keep maps and travel guides out of sight and directions should be sought before embarking on a journey. Bum bags (also known as 'belt bags') should not be recommended as they are highly visible, potential 'one-stop shopping centres' for muggers. Travellers should be advised to keep passport and valuables in a neck wallet, a breathable polycotton pouch capable of holding valuables out of sight under the traveller's shirt. Alternately, they may choose to use a hidden money belt, and a few dollars hidden in a shoe could be enough to hire a taxi to the nearest police

station or back to the hotel. Travellers should be advised to keep copies of important documents and card numbers separately, and also with friends/family at home, in case of theft or loss [62].

Criminals have been known to befriend, drug and rob travellers on trains and buses or even in hotels. This is a worldwide problem. Travellers should be advised to never accept food and drinks from strangers. It is also important that travellers avoid inviting newfound friends to their hotel room. Travellers should not open hotel doors to unannounced strangers or hotel staff, without checking with reception desk staff first. Sexual assault is not uncommon in this type of scenario and advice concerning the potential use of a post-exposure HIV prophylaxis starter pack may be needed in some traveller groups to high risk areas, e.g. students on overseas electives [63]. Travel health advisers should also note that departments of foreign affairs often have advice available for victims of sexual assault, such as a brochure compiled by a governmental organisation in Australia [64]. Post-exposure prophylaxis starter kits may also be useful for health professionals going to work in high risk areas for HIV [63] in the event of percutaneous exposure incidents.

Travellers should be advised to avoid resisting if mugged, since it is better for travellers to give up their wallet rather than their life. If travellers are injured following a mugging, they should be advised to seek medical attention and to report the mugging to the relevant authorities. Travellers should keep receipts for medical treatment. All such criminal incidents should be reported to local authorities and copies of police reports should be kept for travel insurance claims. Most countries have tourist police units, primarily to combat heavy criminal activity against tourists [65]. Travellers should seek advice from their travel insurance and assistance company as soon as practicable. Travellers or their relatives or friends should also advise their embassy, consulate, high commission or foreign affairs department of serous incidents.

Those travellers who may be seeking work abroad should be advised to be vigilant for scams. In particular, travellers should be made aware that the slave trade, including the sex slave trade, still exists in some countries. Even some women from western countries have found themselves virtually captured by their employers, who have taken their passports. Travellers going to work abroad should also be advised not to surrender their passports to anyone, except authorised authorities.

Security issues

Travellers should avoid travelling alone, but at the same time they should be advised to be careful of becoming involved with those travellers who are engaged in any type of illegal activities. If the traveller is spending considerable time in a country or area, particularly one that is off the beaten track or experiencing instability, they should be advised to inform their family and embassy or diplomatic mission of their arrival and itinerary, in the event of any problems. Travellers should be advised to stay in contact with friends and family at home and let them know their location and that they are well. They should also be advised to consider hiring or taking with them a mobile phone, if possible. Group tours with professional expedition organisations should be suggested to travellers going to remote areas.

Personal security is also an issue in many popular tourist areas and there may be a significant risk of theft. A number of hotels and tourism agencies advise travellers about personal safety and travellers should heed this advice. Many travellers' protective devices are available, but travellers should be advised that they should check with local authorities or diplomatic missions to see if they are legal. Weapons, such as guns and knives, should not be carried at any time [62].

Transport safety

Driving

Injury-prevention strategies for travellers, which can be communicated by travel health advisers, have been well-described elsewhere [66] and are summarised in part in Table 33.2. Travellers should be advised to take extreme care while driving abroad and be particularly aware of changed traffic conditions, whether a driver or a pedestrian, as vehicles may drive on the opposite side of the road. Travellers should be advised to heed road rules, avoid speeding and be cautious of the local driving culture [4]. Many travellers will also ride push-bikes or motorbikes abroad. Precautions when riding push-bikes or motorcycles include wearing helmets and other protective clothing to minimise the risk of injury. Wearing helmets alone can reduce head injuries by up to 73% [8]. It may mean that travellers need to be encouraged to take this personal protective equipment with them, especially if it is not provided with the rental bike abroad, as many countries do not legally require these to be worn or provided.

The importance of hepatitis B vaccination in the pre-travel health consultation is illustrated in an Australian study of travellers to East Asia and Southeast Asia, where nearly half of travellers reported being involved with at least one activity with a hepatitis B risk, e.g. 24% reported riding a motorbike or using an off-road vehicle [67]. Travellers should use only reliable, scheduled/official tour and bus services.

Table 33.2 Traffic safety tips for travellers*

For pedestrians:
- Look both ways before crossing the road; remember the traffic may be going on the 'wrong' side of the road
- Don't presume the traffic will stop for you on a crossing
- Watch your belongings; carry as little as possible with you
- Only travel with licensed taxi companies

For drivers:
- Carry an international licence and your own licence for local police (some hire car companies may require international licences in some countries)
- Take reliable maps with you marked in English and local language if possible; if possible purchase a local driving guide
- Let someone know where you are going
- Know the local language for the phrase: which way to . . . ?
- Don't travel alone, if possible; think of alternative transport
- Hire a car or motor bike from a reputable company with safety features installed in vehicles and with comprehensive insurance
- If travelling with young children, make enquiries about child safety seats in rental vehicles. Can they be fitted safely?
- Check vehicles before driving; is it safe? Is there a good spare tyre and jacking equipment
- Wear a helmet when riding a motorbike, bicycle or horse
- Use safety features such as seat belts when driving
- Consider safety requirements of any pets travelling with you (don't forget the pets left at home!)
- Observe speed limits suitable for the conditions
- Don't drink and drive or take other drugs that may interfere with driving
- Find out the local traffic rules and adhere to them
- Consider taking/hiring a mobile phone, where possible, for extended road trips in unfamiliar areas and have a contact number, e.g. for a breakdown service or hire car company

*Reproduced with permission from Leggat PA, Goldsmid JM (eds.) (2005) *Primer of Travel Medicine*, 3rd revised edn. Brisbane, ACTM Publications, Brisbane.

Table 33.3 Summary of various sectors of recommendations for water safety and drowning prevention for travellers (after Cortes *et al.*) [69]

- Investigate exposure to water, presence of pool fencing and lifeguards
- Learn cardiopulmonary resuscitation (CPR)
- Identify the availability of portable flotation devices or bring them with you for a variety of water-related activities
- Ensure boating safety, including boating training and safety equipment, is at a high standard
- Swimming, drowning survival/water rescue skills and scuba training as appropriate
- Swimming in designated swimming areas; get advice on local hazards
- Feet first entry into the water
- Children to swim only under supervision of an adult, who is sober and has CPR training
- Sober boating, swimming and diving

Rental cars can be particularly vulnerable to robbery, car-jacking and attack, particularly those that have distinguishing features in terms of colours, advertising and specialised licence plates. Travellers should be advised to hire vehicles from reputable rental car companies and to carefully examine the vehicle to ensure it appears road-worthy. Hire vehicles, which are security rated, including central and/or computerised locking, engine immobilisers, reinforced safety glass ('armour' glass), mobile phone, and vehicle identification and/or tracking, are preferred. Although a foreign driver's licence may be accepted by rental car agencies, an international driver's licence should be obtained before departure, which may assist when dealing with local authorities, as well as acting as a secondary form of identification.

Travellers should be advised to get directions before setting off or be shown how to use satellite navigation devices installed in their vehicles, and travel only on major routes, unless travelling with reliable guides. Driving alone and driving at night should be avoided in unfamiliar countries [62]. While travelling, travellers should be advised to keep all doors locked with windows wound up, especially when stopped at traffic lights. Extra care needs to be taken with all luggage, and valuables should be placed out of sight, especially while the vehicle is unattended. Individuals travelling with their own domestic pets should also take appropriate precautions for their animals [68] and should be advised that many countries have road rules requiring animals to be restrained in motor vehicles.

Ferries

Travellers should be advised to use only reliable, scheduled and official ferry and tour boat services. Travellers should be wary of taking ferry and tourist boat trips at night or with storms or bad weather pending.

Water safety

Detailed consensus recommendations concerning water safety and drowning prevention have been published elsewhere [69]. Table 33.3 summarises the broad recommendations.

Swimming

Many countries, such as Australia, promote water-related recreational activities [70]; however, the water is often an unfamiliar environment for international tourists [71]. For these travellers and visitor groups, water safety remains a priority area for the pre-travel health consultation and worthy of mention in travel advisories. In relation to water safety, identifying those travellers and visitor groups who are potentially 'at risk' should assist health and tourism authorities to present appropriate water safety information in the language of the target group and to ensure this information is made available to visitors before they leave home and when they arrive [26]. This was supported by a review of coronial inquests in Australia, which concluded that: 'Static signage and general safety information brochures will only be effective if they are drawn to the attention of visitors, ideally before, or at least on arrival, at the particular destination' (p. 52) [72]. This parallels the issues in scuba diving where the focus in recent years has been ensuring that an appropriate assessment of medical fitness of divers is conducted before diving [73]. Although yet to be formally evaluated, particularly for other at-risk groups, examples of significant tourist water safety initiatives undertaken by Surf Life Saving Australia for the Japanese inbound market have been described elsewhere [74]. Wider public access to semi-automated external defibrillators, including among surf lifesaving and other first responder groups, may also assist travellers [75].

Water sports

Travellers should be advised to use only reliable, scheduled and official water sports services. Travellers should be well briefed by operators on safety procedures of the particular water sports and operators should ensure as far as possible the safety of tourists. Travellers should check to ensure that their travel insurance would cover them in the event of mishaps while participating in more extreme water sports, such as parasailing, jet boating and jet skiing, as these activities are frequently not covered [76]. Local authorities need to create watercraft exclusion zones in popular swimming and water sports areas close to shore. Similarly, watercraft involved with water sports should be regulated and speed limited in swimming areas.

Marine bites and stings

Travellers should be advised to seek local advice before going swimming, and heed the advice of surf lifesaving groups or water police, where these exist. Swimming should be avoided in isolated areas where marine hazards such as sharks and stingrays have caused death and severe injury to tourists [77, 78]. For example, the message must be communicated that those enjoying the expansive coastal beaches of Australia should swim in areas patrolled by the iconic surf lifesavers [79]. Local advice and heeding local warning signs may be important for tourists in avoiding marine envenomation [80]. An Australian study of travellers visiting north Queensland found that only 34% of international travellers had knowledge of the Irukandji, a potentially lethal jellyfish found across the northern coastline of Australia [80]. A major contributor to this was that less than half (46%) of international travellers had received pre-travel health advice before coming to Australia [80]. Knowledge of basic first aid can be useful in assisting with near-drowning incidents and marine envenomation [69].

Wildlife parks and nature reserves

Wildlife parks

Those travelling through wildlife parks, especially in Africa, should seek advice from their travel agent and foreign affairs officials concerning safety in the reserves they intend travelling through [81]. An increase in armed conflicts, especially in northeastern and central Africa, has made military automatic and semi-automatic weapons easily available in many African countries for use in robberies and attacks. Travellers have also occasionally encountered life-threatening situations from wild mammals, although, fortunately, attacks on tourists by wild mammals, at least in South Africa, appear to be an uncommon cause of injury and death [82]. Travellers should be advised to remain in their vehicles while driving through wildlife reserves and to seek the assistance of a qualified guide or park ranger if they wish to explore on foot [81, 82].

Nature reserves

Travellers should also take care when trekking, rock climbing and mountaineering in national parks, and ensure that they take appropriate safety measures, especially in remote and hazardous areas. Travellers should be aware that weather conditions can change quickly and ensure that they carry survival kits in particularly remote areas. Local authorities should ensure that tourists are excluded from any areas in national parks that are unstable or under construction and keep registers to track all tourists in the larger nature reserves.

Contingency planning

Despite the best advice, preparations and prophylaxis regimens, travellers can be compromised in respect of their

Table 33.4 Websites for some major travel advisories*

Top hits on a google.com search
- US State Department, http://travel.state.gov/
- Foreign Affairs Canada, http://www.voyage.gc.ca/
- Foreign Affairs Australia, http://www.smartraveller.gov.au/
- Foreign Affairs New Zealand, http://www.safetravel.govt.nz/
- Foreign and Commonwealth Office UK, http://www.fco.gov.uk/en/travel-and-living-abroad/

Others
- Central Intelligence Agency World Factbook, https://www.cia.gov/library/publications/the-world-factbook/

*All accessed 18 January 2010

health, safety and security when travelling abroad. For this reason, the travel health adviser should strongly advocate the use of safety nets by travellers. Apart from keeping up to date with national travel advisories for the destinations they are going to, these safety nets mostly relate to uptake of travel insurance. Travel insurance provides for health insurance and insurance for travel and belongings in the event of misadventure, but just as importantly reputable travel insurance providers ensure that travellers have access to a 24-hour emergency assistance service, which may assist them in finding or even coordinate medical care and organise aeromedical evacuation services if needed.

Travel advisories

National government travel advisories have assumed great importance for informing the security, safety and health of international travellers [54]. In addition to being discussed during the pre-travel health consultation, travellers should ensure that they check travel advisories prior to departure. Websites for some of the major travel advisories are given in Table 33.4.

Travel insurance

Travel insurance is the most important safety net for travellers in the event of misadventure, and the purchase of travel insurance should be reinforced by travel health advisers. Only 4% of GPs in a late 1980s study in the UK would advise a traveller going to Turkey about travel insurance [83]. More recent studies, however, have shown about 60% of GPs in New Zealand [56], 39% of GPs in Australia [57] and 39% of travel clinics worldwide [58] usually advised travellers about travel insurance. Nonetheless, it is not known what proportion of travel agents or airlines give advice routinely on travel insurance. And, it is not clear that all travel insurance is adequate for the emergent needs that travellers might face [84].

Travel insurers normally underwrite travel, medical and dental expenses incurred by travellers abroad and arrange aeromedical evacuation of travellers under specified conditions. Medical and dental claims make up more than two-thirds of all claims [43]. Travellers should be advised to read their policies carefully to see what is covered, the level of the excesses, and to check for any exclusions. In particular, those travellers who have known pre-existing conditions, who are working long-term overseas, or who are going to undertake any form of hazardous recreational or occupational pursuit may need to obtain a special travel insurance policy, and this may attract a higher premium [76].

In addition, travel insurance companies often provide a service, usually through their emergency assistance contractors, to assist travellers abroad. This may include assisting with medical care while overseas, including aeromedical evacuation. Use of the emergency telephone service provided by the travel insurance company was reported in almost one-fifth of claims in a study of general claims in Australia [85]. In a recent Swiss study, more than two-thirds of claims made through the travel insurer's assistance centre were for illness, while the remainder were due to accidents [11].

Medical kit

Travellers should routinely be advised to carry a travel medical (or 'first aid') kit, which should be customised to their anticipated itinerary and activities. They should include basic health information (name, birth date, vaccination history, current medication use – with dosages noted, known medical allergies, blood type and chronic health conditions). Antiseptic solutions and lotions, bandaging supplies and perhaps splinting material should also be included. Obviously, adventurous travellers engaging in strenuous physical activity far from medical care should take along more extensive first aid supplies. The traveller could include common healthcare products such as sunscreen and insect repellent. Routinely used over-the-counter medications (antipyretics, analgesics, topical anti-inflammatory and anti-pruritic skin creams, and antihistamines) should also be included. Routine prescription medications should be included, with a second supply of important or unusual medicines in another part of the luggage in case the traveller is separated from some bags en route. Some presumptive-use medications should also be placed in the medical kit, including items such as antimalarial and antidiarrhoeal medications as well as oral rehydration salts. Caution with needles and quantities of liquids needs to be observed when clearing airport security, and local advice should be obtained.

Emergency assistance

Medical and dental care also does not tend to be as accessible in the public health systems of many developing countries; however, private clinics may be found. There may, however, be language barriers that need to be overcome. If possible, before travel, it may be helpful to provide travellers with a recommendation for suitable medical treatment services at their destinations, particularly if they are prone to medical problems. Ideally, their travel health adviser should give this recommendation, together with a letter outlining the traveller's medical history. It is salient to advise travellers with chronic health conditions to wear Medical Alert (www. medicalert.org) identification in case emergency healthcare is required while abroad. Such identification will enable a healthcare professional to access medical information about the traveller in the event of an emergency. Once travelling, recommendations concerning suitable doctors available for consultation while overseas may be obtained from foreign missions, hotels, private hospitals and travel clinics. Only about half of GPs in New Zealand usually advised travellers about finding medical assistance abroad and only about one-fifth of GPs recommended travel insurance companies, as a source of medical assistance while travelling [56]. In Australia, about two-fifths of GPs would normally advise about travel insurance [57].

Even life-threatening conditions are often managed surprisingly well in rather underdeveloped medical systems [86]. Travellers, however, can be prepared to best make use of overseas medical resources if they keep in mind some key 'rules of the road' [87]:

- do not assume that the healthcare system is at all similar to the one you left at home
- seek out units that have a reputation of caring for foreigners
- clarify payment issues from the start
- make the doctors/nurses comfortable and willing to help you
- avoid leveraging knowledge from you home country in the hopes of 'educating' the local providers about what needs to be done
- understand that in some cultures, questions from patients or family members are often perceived as challenges to the authority of the doctors
- decide which issues you will try and influence and which you are going to leave alone
- have 'exit strategies' prepared in advance that allow you to bow out gracefully from the care if you are dissatisfied
- watch for incentives for people directing your care
- carefully consider evacuation/travel insurance.

The literature also lists possible sources of insurance [87].

Travel insurance and other agencies often provide a service to assist travellers in finding medical care while overseas and may be able to assist with providing information on the medical history of the traveller in an emergency. The most common advice required from the insurer's emergency assistance service relates to claiming and policy information [85]. Further, the need for emergency room review or hospitalisation was required for about one-sixth of those using the emergency assistance service [85]. Aeromedical evacuation was an uncommon and expensive form of emergency assistance, but was indicated for only a small number of travellers [85].

Search and rescue

Travellers should be reminded that not all countries have advanced search and rescue (SAR) capability on call. A study by Heggie and Amundson in the US found that one in five (20%) of those requesting SAR would have perished without a response [88]. Hiking (48%) and boating (21%) were the activities most frequently requiring SAR [88]. Travellers need to be reminded that SAR is an expensive exercise and that some authorities seek compensation from rescued individuals. Travellers should therefore be cautious about their travel to wildlife parks and nature reserves, especially in very remote locations, and to go with a well-equipped and experienced expedition group.

Aeromedical evacuation

Aeromedical evacuation/retrieval is a planned activity that requires careful assessment and preparation of the patient. A little time spent prior to the evacuation will make the entire procedure much smoother and less prone to complications. Escorts need to be trained health professionals who are familiar with equipment on aircraft used for aeromedical evacuation. Evacuation may be performed on a conventional commercial flight or on a specially fitted out aircraft, either a fixed-wing aircraft or a helicopter. The latter are usually maintained by emergency services (air ambulance), the military, multinational companies and also by international travellers' assistance organisations. Every evacuation should be carefully considered since they are costly both in terms of time and resources. International aeromedical evacuations can cost US$50,000–100,000 or more. All travellers therefore should take out appropriate travel insurance that covers against this contingency, but should also use common sense to ensure that the need for aeromedical evacuation is keep to a minimum [89].

Air travel may not be appropriate with certain medical conditions (e.g. pneumothorax, decompression sickness,

head injuries) if other options are available. Location and transport availability may also affect choice of mode of transport. Aeromedical evacuations are also conducted on scheduled commercial aircraft by modifying the cabin space prior to flight. Most airlines have medical policies concerning aeromedical evacuations. If in the future aeromedical evacuation modules are to be installed on scheduled airlines, then it might be easier to evacuate travellers using a scheduled civilian flight. A dedicated air ambulance will be used in some instances. The air ambulance selected must have adequate range, available service areas, reasonable speed, adequate cabin space and adequate medical equipment for the journey [89].

Conclusion

Clearly, many cases of death and life-threatening injury and illness could be prevented. Preventive strategies should be discussed at pre-travel consultations. Emphasis should be placed on road and water safety as well as on the 'usual' travel medicine topics of malaria, diarrhoea and vaccination. Realising that adverse events can occur during travel, travellers should be armed with appropriate insurance and a clearly outlined plan for dealing with medical emergencies. When necessary, appropriate evacuation can be employed to get the sick or injured traveller to a more specialised medical care setting.

References

1. Steffen R (2008) Epidemiology: morbidity and mortality in travelers. In: Keystone JS et al. (eds) *Travel Medicine*, pp. 5–11. Mosby, Elsevier, St Louis, MO.
2. Nothdurft HD and Caumes E (2013) Epidemiology of health risks and travel. In: Zuckerman JN (ed.) *Principles and Practice of Travel Medicine*, 2nd edn, pp. 19–26. Wiley, Chichester.
3. Prociv P (1995) Deaths of Australian travellers overseas. *Med J Aust* **163**: 27–30.
4. MacPherson DW *et al.* (2000) Death and dying abroad: the Canadian experience. *J Travel Med* **7**: 227–233.
5. Hargarten SW and Grenfell RD (2001) Travel-related injuries (motor vehicle crashes, falls, drownings): epidemiology and prevention. In: Dupont HL and Steffen R (eds) *Textbook of Travel Medicine and Health*, 2nd edn, pp. 371–375. BC Decker, London.
6. Wilks J *et al.* (2003) Accidental deaths of overseas visitors in Australia 1997–2000. *J Hosp Tourism Manag* **10**: 79–89.
7. Bewes PC (1993) Trauma and accidents: practical aspects of the prevention and management of trauma associated with travel. *Br Med Bull* **49**: 454–464.
8. Steffen R *et al.* (eds) (2007) *Manual of Travel Medicine and Health*, 3rd edn. BC Decker, Hamilton, Canada.
9. Eitzinger C and Wiedemann PM (2008) Trust in the safety of tourist destinations: hard to gain, easy to lose? New insights on the Asymmetry Principle. *Risk Anal* **28**: 843–853.
10. Leggat PA and Leggat FW (2003) Reported fatal and non-fatal incidents involving tourists in Thailand. *Travel Med Infect Dis* **1**: 107–113.
11. Somer Kniestedt RA and Steffen R (2003) Travel health insurance: indicator of serious travel health risks. *J Travel Med* **10**: 185–189.
12. Hargarten SW *et al.* (1991) Overseas fatalities of United States citizen travelers: an analysis of deaths related to international travel. *Ann Emerg Med* **20**: 622–626.
13. Court C (1995) Survey highlights risks of foreign holidays. *Br Med J* **310**: 1287.
14. Van der Wal MF *et al.* (1996) Causes of death in Amsterdam children who died abroad, 1982–1993; potential for prevention. *Nederlands tijdschrift voor geneeskunde* **140**: 771–781.
15. Steffen R (1991) Travel medicine: prevention based on epidemiological data. *Trans Roy Soc Trop Med Hyg* **85**: 156–162.
16. Guse CE *et al.* (2007) Fatal injuries of US citizens abroad. *J Travel Med* **14**: 279–287.
17. Tonellato DJ *et al.* (2009) Injury deaths of US citizens abroad: new data source, old travel problem. *J Travel Med* **16**: 304–310.
18. MacPherson DW *et al.* (2007) Death and international travel – the Canadian experience: 1996 to 2004. *J Travel Med* **14**: 77–84.
19. Baker TD *et al.* (1992) The uncounted dead – American civilians dying overseas. *Publ Health Rep* **107**: 155–159.
20. Nicol J *et al.* (1996) Tourists as inpatients in Queensland regional hospitals. *Aust Health Rev* **19**: 55–72.
21. Wilks J and Coory M (2002) Overseas visitor injuries in Queensland hospitals: 1996–2000. *J Tourism Stud* **13**: 2–8.
22. Bentley TA *et al.* (2004) The safety experience of New Zealand adventure tourism operators. *J Travel Med* **11**: 280–286.
23. Ball DJ and Machin N (2006) Foreign travel and the risk of harm. *Int J Injury Control Safety Prom* **13**: 107–115.
24. Uzun I *et al.* (2009) Foreigners dying in Istanbul. *J Forensic Sci* **54**: 1101–1104.
25. McInnes RJ *et al.* (2002) Unintentional injury during foreign travel: a review. *J Travel Med* **9**: 297–307.
26. Wilks J (2004) Injuries and injury prevention. In: Keystone JS et al. (eds) *Travel Medicine*, pp. 453–459. Mosby, Elsevier Science, Amsterdam.
27. Grenfell R (2001) Travel-related injury. In: Zuckerman J (ed.) *Principles and Practice of Travel Medicine*, pp. 291–296. Wiley, Chichester.
28. Thai Ministry of Public Health (2009) Ch. 5 S. 2.6 Injury and Accidents in Thailand Health Profile 2005–2007, http://www.moph.go.th/ops/thp/index.php?option=com_content&task=view&id=6&Itemid=2&lang=en (accessed 18 January 2010).
29. Baldwin A *et al.* (2008) Look right! A retrospective study of pedestrian accidents involving overseas tourists. *Emerg Med J* **25**: 843–846.
30. Steffen R *et al.* (2003) Travel epidemiology – a global perspective. *Int J Antimicrob Agents*: **21**, 89–95.
31. Wilks J (1999) International tourists, motor vehicles and road safety: a review of the literature leading up to the Sydney 2000 Olympics. *J Travel Med* **6**: 115–121.

32. Petridou E *et al*. (1997) Epidemiology of road traffic accidents during pleasure travelling: the evidence from the island of Crete. *Accident Anal Prev* **29**: 687–693.
33. Wilks J *et al*. (2002) Overseas visitor deaths in Australia: 1997–2000. *Curr Issues Tourism* **5**: 550–557.
34. Leggat PA and Wilks J (2009) Overseas visitor deaths in Australia, 2001–2003. *J Travel Med* **16**: 243–247.
35. Shinar D *et al*. (2003) Traffic sign symbol comprehension: a cross cultural study. *Ergonomics* **46**: 1549–1565.
36. Rowden P *et al*. (2008) Road crashes involving animals in Australia. *Accident Anal Prev* **40**: 1865–1871.
37. Morgan D *et al*. (2008) Descriptive epidemiology of drowning deaths in a surf beach swimmer and surfer population. *Injury Prev* **14**: 62–65.
38. Mackie IJ (1999) Patterns of drowning in Australia, 1992–1997. *Med J Aust* **171**: 587–590.
39. Grundy D *et al*. (1991) Diving into the unknown. *Br Med J* **302**: 670–671.
40. Wilks J and Coory M (2000) Overseas visitors admitted to Queensland hospitals for water-related injuries. *Med J Aust* **173**: 244–246.
41. Cornall P *et al*. (2005) Drowning of British children abroad. *Child Care Hlth Dev* **31**: 611–613.
42. Venditto J and Mouzos J (2006) The murder of overseas visitors in Australia. *Trends & Issues in Crime and Criminal Justice*, No. 316. Australian Institute of Criminology, Canberra.
43. Leggat PA and Leggat FW (2002) Travel insurance claims made by travelers from Australia. *J Travel Med* **9**: 59–65.
44. Tutenges S (2009) Safety problems among heavy-drinking youth at a Bulgarian nightlife resort. *Int J Drug Pol* **20**: 444–446.
45. Bellis MA *et al*. (2007) Effects of backpacking holidays in Australia on alcohol, tobacco and drug use of UK residents. *BMC Publ Hlth* **7**: 1.
46. MacPherson DW *et a*l. (2000) Arrest and detention in international travelers. *J Travel Med* **7**: 180–186.
47. DFAT (2009) Australians detailed Overseas-Top detention destinations. 19 May 2009 Cited by Daily Telegraph 23 May 2009, Sydney.
48. Paixao ML *et al*. (1991) What do Scots die of when abroad. *Scot Med J* **36**: 114–116.
49. Anonymous (2004) Malaria surveillance – United States, 2002. *MMWR: Morbid Mortal Wkly Rep* **53**(SS01): 21–34.
50. Thomson MM and Najera R (2001) Travel and the introduction of human immunodeficiency virus type 1 non-B subtype genetic forms into Western countries. *Clin Infect Dis* **32**: 1732–1937.
51. Stewart L and Leggat PA (1998) Culture shock and travelers. *J Travel Med* **5**: 84–88.
52. Valk TH (2008) Psychiatric disorders and psychiatric emergencies overseas. In: Keystone JS *et al*. (eds) *Travel Medicine*, pp. 367–377. Mosby, St Louis, MO.
53. Thomas RE (2000) Preparing patients to travel abroad safely. Part 4: reducing risk of accidents, diarrhea, and sexually transmitted diseases. *Can Fam Phys* **46**: 1634–1638.
54. Leggat PA (2006) Risk assessment in travel medicine. *Travel Med Infect Dis* **4**: 127–134.
55. Behrens RH (1990) Protecting the health of the international traveller. *Trans Roy Soc Trop Med Hyg* **84**: 611–612, 629.
56. Leggat PA *et al*. (1998) Safety advice for travelers from New Zealand. *J Travel Med* **5**: 61–64.
57. Seelan ST and Leggat PA (2003) Health advice given by general practitioners for travellers from Australia. *Travel Med Infect Dis* **1**: 47–52.
58. Hill DR and Behrens RH (1996) A survey of travel clinics throughout the world. *J Travel Med* **3**: 46–51.
59. Leggat PA (1997) Travel health advice provided by inflight magazines of international airlines in Australia. *J Travel Med* **4**: 102–103.
60. Leggat PA *et al*. (2007) Hostelers' knowledge of transmission and prevention of avian influenza when travelling abroad. *Travel Med Infect Dis* **5**: 53–56.
61. Leggat PA *et al*. (2007) Level of concern and sources of information of a group of Brisbane hostelers for personal safety and terrorism when traveling abroad. *J Travel Med* **14**: 112–116.
62. Leggat PA and Klein M (2001) Personal safety advice for travelers abroad. *J Travel Med* **8**: 46–51.
63. Richens J (2006) Sexually transmitted infections and HIV among travelers: a review. *Travel Med Infect Dis* **4**: 184–195.
64. Department of Foreign Affairs and Trade, Canberra, Australia (2011) Sexual Assault Overseas, http://www.dfat.gov.au/consular/sexualassault.html (accessed 22 May 2012).
65. Spira AM (2006) Preventive guidance for travel: trauma avoidance and medical evacuation. *Disease a Month* **52**: 261–288.
66. Hargarten SW (1994) Injury prevention: a crucial aspect of travel medicine. *J Travel Med* **1**: 48–50.
67. Leggat PA *et al*., Travel Health Advisory Group (2009) Hepatitis B risks and immunisation coverage amongst Australians travelling to Southeast and East Asia. *Travel Med Infect Dis* **7**: 344–349.
68. Leggat PA and Speare R (2000) Traveling with pets. *J Travel Med* **7**: 325–329.
69. Cortes LM *et al*. (2006) Recommendations for water safety and drowning prevention for travelers. *J Travel Med* **13**: 21–34.
70. Wilks J and Atherton T (1994) Health and safety in Australian marine tourism: a social, medical and legal appraisal. *J Tourism Stud* **5**: 2–16.
71. Wilks J (ed.) (2008) *Beach Safety and the Law: Australian Evidence*. Surf Life Saving Australia, Sydney.
72. Wilks J (2006) Coroners' concerns about international visitor deaths in Australia. *Int Travel Law J* **13**(1): 42–52.
73. Wilks J (2000) Scuba diving and snorkeling safely on Australia's Great Barrier Reef. *J Travel Med* **7**: 283–289.
74. De Nardi M and Wilks J (2007) Tourist water safety: surf Life Saving initiatives for the Japanese inbound market. *J Vacation Mkting* **13**: 275–283.
75. Leggat PA *et al*. (2003) First aid and travellers. *Travel Med Infect Dis* **1**: 141–143.
76. Leggat PA *et al*. (1999) Travel insurance and health. *J Travel Med* **6**: 252–257.
77. Shaw M and Leggat PA (2003) Country profile: travelling to Australia. *Travel Med Infect Dis* **1**: 126–133.
78. Diaz JH (2008) The evaluation, management, and prevention of stingray injuries in travelers. *J Travel Med* **15**: 102–109.
79. Wilks J *et al*. (2005) Tourists and beach safety in Queensland, Australia. *Tourism Marine Environ* **1**: 121–128.

80. Leggat PA *et al.* (2005) Health advice obtained by tourists travelling to Magnetic Island: a risk area for 'Irukandji' jellyfish in North Queensland, Australia. *Travel Med Infect Dis* **3**: 27–31.
81. Leggat PA *et al.* (2001) Traveling in wildlife reserves in South Africa. *J Travel Med* **8**: 41–45.
82. Durrheim DN and Leggat PA (1999) Risks to tourists posed by wild mammals in South Africa. *J Travel Med* **6**: 172–179.
83. Usherwood V and Usherwood TP (1989) Survey of general practitioners' advice for travellers to Turkey. *J Roy Coll Gen Pract* **39**: 148–150.
84. Grace RF and Penny D (2004) Travel insurance and medical evacuation: view for the far side. *Med J Aust* **80**: 32–35.
85. Leggat PA *et al.* (2005) Emergency assistance provided abroad to insured travellers from Australia. *Trav Med Infect Dis* **3**: 9–17.
86. Aldis JW (2004) Healthcare abroad. In: Keystone JS *et al.* (eds) *Travel Medicine*, pp. 461–467. Mosby, St Louis, MO.
87. Kolars JC (2002) Rules of the road: a consumer's guide for travelers seeking health care in foreign lands. *J Travel Med* **9**: 198–203.
88. Heggie TW and Amundson ME (2009) Dead men walking: search and rescue in US National Parks. *Wild Environ Med* **20**: 244–249.
89. Leggat PA and Aitken P (2006) Travel insurance and aeromedical retrieval. In: Wilks J *et al.* (eds) *Tourism in Turbulent Times: Towards Safe Experiences for Visitors*, pp. 37–52. Elsevier, London.

Chapter 34 The international athlete: travelling healthy to global sporting events

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Introduction

The contemporary athlete is a global traveller [1]. The 2004 Summer Olympic and Paralympic Games in Athens attracted an estimated 25,000 athletes and support staff from 201 countries and serves as good example of the interest high-profile international sports receive [2]. Even lower-profile recreational sports such as marathons, triathalons and golf are attracting more and more athletes willing to travel long distances to compete [3]. Depending on the sport, these competitions range in duration from one day to several weeks and often represent the ultimate challenge for participating athletes. However, a fact that is often overlooked is that the nature of international travel poses obstacles to the health, safety and maximum performance of athletes.

Pre-travel planning

Athletes are under considerable pressure to perform at the highest level in every competition in which they participate. For the contemporary athlete, the nature of international travel presents athletes with added obstacles to their pre-competition preparation. Thus, it is increasingly important to address these obstacles prior to travel. This is especially important given that today's athlete will likely need to travel on a regular basis to compete in the global arena of competitive sport [3]. Moreover, preparation is important because an athlete's training can easily be undone if all aspects of travel have not been considered.

Preparation for sports-related travel includes pre-travel health issues [4, 5]. Most athletes and sports teams will have their own medical plans for deployment to an international event. However, it is still important that their travel health advisers are prepared to discuss preventative health issues with all officials and athletes travelling to an athletic competition. Such issues are best discussed by way of a checklist of 'items to be discussed' and include personal health issues such as those of a dental and sexual health nature, coping with acclimatisation and jet lag, coping with culture shock and managing personal stresses due to the altered environment, immunisations, female-specific health issues, diet, medical kits and other general travel health issues [6]. In addition, it is important to recognise that it is not just the athlete that will need to be adequately prepared for travel. All members of the coaching staff, medical team and support staff will also need to be wary of any health implications of their travel abroad [3]. It is therefore prudent that a well-designed plan of action is developed well in advance of any intended travel. This plan of action should include travel preparation (including an understanding of the culture of the intended countries of travel), in-travel experiential health, pre-competition training on arrival at a destination, the competition environment, and the post-competition mindset of the victor and the vanquished [3].

Pre-travel medical assessment

Pre-travel screening assessments and examinations should be mandatory for all athletes and the preparations for these should begin as early as possible. This will help facilitate insurances and give an indication of ongoing medical concerns that may need to be specifically evaluated before departure. These concerns can range from allergies (including any of environmental provocation), asthma, cardiac conditions and dental caries to diabetes, gastroenterological concerns and locomotor or neurological concerns. In addition, early assessment on the part of the medical team will aid the development of an athlete's exercise routine and also allow adequate preparation time for specific travel-related medical requirements such as vaccinations, antimalarials and other medications. It will also provide adequate time to

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find out about the local medical facilities at an intended destination [3, 6].

As with all consultations, full documentation is to be advised with copies of all assessment forms and any appropriate lab and radiology data. A record of an athlete's pre-travel information will also need to include any medications prescribed and what they are prescribed for. This 'personal travel health record' is an essential part of the medico-legal documentation of any athlete as it is an aid to ongoing management in a foreign country [3]. Nevertheless, certain medications are not permitted into some countries and it would be prudent for all athletes and their medical staff to consult the travel restrictions and customs websites of destination countries.

It is also helpful to assume that no ongoing arrangements have been made at a destination venue and that the athlete must be guided into a rigid itinerary. This will help remove any confusion about what the athlete is to do on arrival. Such an itinerary will be determined by whether an athlete is part of a team or is travelling alone. To this end, medical assessors need to communicate well ahead of time with the host venue or its medical staff to determine the facilities available to them. It is undoubtedly appropriate that the medical assistant to the athlete does this because it will help reduce pre-travel stress on the athlete and enable them to train with an uncluttered focus. It also gives medical personnel the chance to determine the level of medical capabilities in any intended venue and the level of provisions available to the athlete [3].

Preparing medical kits

Providing medical assistance for an athlete or group of athletes requires one to be prepared with a variety of supplies and medications [3]. Determining the necessary supplies and equipment to take to international competitions can be a difficult task [7]. In addition, it is best to strive for self-sufficiency and assume nothing will be provided at the competition site [7]. Tables 34.1 and 34.2 provide examples of a medical kit and a personal medication kit for individual athletes. It should be noted that the contents of Tables 34.1 and 34.2 are recommendations only [8–10]. Individual circumstances may dictate making changes to a medical kit.

A hard-sided medical kit is recommended to best withstand travel through airports and general transportation [3]. It is also recommended that a list of all the supplies be kept within the kit, and that the head athletic trainer or team physician keeps a personal copy of the list for clearing customs and airport security purposes [3]. In regard to athlete medication, all medications should be labelled in their appropriate container and a doctor's letter or copy of the original prescription should be taken for each medication [4].

Long-distance travel to sporting venues

International travel for training and competition is an essential part of the life of elite athletes [11]. It is also becoming increasingly common among recreational sports persons as they seek greater personal challenges. Long-distance travel can create physiologic disturbances and psychological stresses that can potentially interfere with athletic performance. Regardless of the mode of transportation, today's combination of airport lines, flight schedules, increased airport security, ground transportation and lodging arrangements, food concerns and pre-competition anxiety highlights the importance of pre-travel planning. Arriving at airports early, flying familiar airlines that serve familiar foods, making arrangements for special food services with airlines and reserving preferred seating or special seating for physically disabled athletes can help minimise travel stress. Adequate rest and nutrition prior to flying will also help to alleviate travel stress [11].

Long-haul health consequences

One of the major health risks associated with long-haul flights is deep vein thrombosis (DVT) [12, 13]. This condition can be provoked by athletes remaining immobile or in restricted postures during long flights. This in turn aids the formation of clotting in leg veins or in the deep veins of the pelvis. The classical symptoms of DVT include pain, swelling and redness of the leg, and dilation of the surface veins. The prevention of DVT is aided by athletes walking around the cabin of a plane frequently, by performing isometric exercises while seated, and wearing compression stockings [3, 13]. The use of aspirin to prevent DVT on long-haul flights has not been substantiated [11].

Jet Lag

Long-distance travel is associated with jet lag, a term that reflects transient negative effects that result from anxiety about the intended journey, change to an individual's daily routine and subjective feelings of dehydration due to time spent in the low humidified dry air of an aircraft cabin [14, 15]. Jet lag occurs when there is desynchrony between normal daily rhythms (the body's internal clock) and the new light–dark cycle caused by abrupt time zone changes at the destination [16–18]. Jet lag is a condition whose effects may last many days or weeks, depending on the number of time zones

Table 34.1 Suggested items for a team medical kit

Diagnostic items

Stethoscope, sphygmomanometer, peak flow meter, ophthalmoscope, auriscope, digital thermometer, penlight, Snellen visual chart, lubricating jelly, ophthalmic anaesthetic drops, examination gloves (various sizes), tongue depressors, fluorescein airdrops or eye-strips, vaginal speculum, blood glucose test unit and strips, proctoscope

Documentation items

Medical record cards, letterhead paper, pens

Therapeutic items: physical treatments

- Scissors, forceps, artery forceps, disposable suture set, variety of suture material (both synthetic and gut), Steri-Strips

Local anaesthetic – with and without adrenaline, syringes (1, 3, 5, 10, 30 ml) and needles (18 g, 21 g, 23 g, 25 g, 27 g)
Dressing materials, cotton buds
Cold packs
Tinc benzoin solution
Bandages (triangular, compressive)
Splints: finger, arm, leg, neck
Zinc oxide tape
Ear syringe
Electromedical equipment – physio

Therapeutic items: medicinal

NOTE: Some of these medications are banned by the World Anti-Doping Agency (WADA). Before administering them, for valid medical indications, the athlete needs to be fully informed of any possible consequences. WADA and the athlete's sport management body may also need to be informed. A record of all medications administered needs to be up to date and maintained.

Injectable

Adrenaline 1:1000, atropine
Furosemide (frusemide)
Tramadol, diclofenac, morphine or pethidine
Metoclopramide, prochlorperazine
Verapamil
Sumatriptan
Diazepam
Chlorpromazine
Promethazine
Hyoscine
Triamcinolone
Lignocaine
Fluids – 50% dextrose, water for injection

Oral

Cardiovascular: nitroglycerin (glyceryl trinitrate) spray, furosemide, isosorbide mononitrate, atenolol
Gastrointestinal: antacids, omeprazole, metoclopramide, dicycloverine (dicyclomine), loperamide, docusate sodium
Musculoskeletal: diclofenac
Sedatives: temazepam, zopiclone
Antibiotics: amoxicillin, amoxicillin/clavulanic acid, doxycycline, tinidazole, flucloxacillin, phenoxymethylpenicillin (penicillin VK), azithromycin erythromycin, cotrimoxazole, clarithromycin, ciprofloxacin, norfloxacin
Respiratory: inhalers – terbutaline, budesonide, nedocromil, pholcodine elixir; sprays – xylometazoline, budesonide
Renal (urinary alkaliniser): norfloxacin, trimethoprim
Neurological: paracetamol/metoclopramide, sumatriptan, prochlorperazine
Psychiatric/anxiolytic: chlorpromazine, lorazepam sublingual
Allergy: loratadine
Eyes: chloramphenicol drops and ointment, ocular decongestant drops
Ears, nose, throat: corticosteroid/antibacterial drops, ipratropium spray, benzydamine lozenges, triamicinolone in dental paste, ear wax drops, acetic acid drops
Skin: corticosteroid creams – very potent (e.g. Dermovate), potent (e.g. Betnovate), moderate strength (e.g. Eumovate), 1% hydrocortisone; mupirocin ointment; aciclovir cream; fucidin cream; miconazole cream
Gynaecological: clotrimazole cream and pessaries, norethisterone tablets
Rectal: corticosteroid with local anaesthetic ointment and suppositories, bisacodyl suppositories, disposable tube enemas
Analgesics: aspirin, paracetamol, nefopam, tramadol
Contraception: condoms, post coital contraceptives (e.g. ethinyloestradiol plus norgestrel)

Source: adapted from Milne, 1996; Shaw and Dallimore, 2005; Whatley and Barbeau, 2010 [8–10].

Table 34.2 Suggested personal medications for individual athletes

Medicines
- Personal prescription medication. Preferably two caches in two different parts of the luggage in case one gets lost
- Personal anti-allergy medication, where there is a history of severe allergy

Special note about prescription medicines
- Take a letter from your supervisory medical practitioner, noting the medications you are on and why you are taking them. This is especially so for controlled substances and injectable medications. This letter should be on letterhead stationery
- Pack one cache of your prescription medications in your carry-on luggage
- Take copies of all prescriptions. They should include the generic names for all medications
- Leave a copy of your prescription medications with your family or friend and give one to the team doctor

Special prescriptions for the trip
- Medicines to prevent malaria, if required
- Antibiotic prescribed by your doctor for self-treatment of moderate to severe diarrhoea, respiratory tract infections, skin and minor trauma infection and injury. Note that the doctor should include instructions on when to take the medication, and how to use it appropriately

Over-the-counter medicines
- Anti-diarrhoeal medication (for example, oral rehydration salts, loperamide)
- Antihistamine
- Decongestant, alone or in combination with antihistamine
- Anti-motion sickness medication
- Medicine for pain or fever (such as paracetamol, aspirin or ibuprofen)
- Mild laxative
- Cough suppressant/expectorant
- Cough drops
- Antacid
- Antifungal and antibacterial solutions, ointments or creams
- 1% hydrocortisone cream, with or without antibacterial additives

Other important items
- Supplies to prevent illness or injury
  - insect repellent containing DEET (30%-50%) or picaridin (up to 25%)
  - sunscreen (preferably SPF 15 or greater) with both UVA and UVB protection
  - antibacterial hand wipes or alcohol-based hand sanitizer containing at least 60% alcohol
  - lubricating eye drops
- First-aid supplies
  - first aid quick reference card
  - basic first-aid items (bandages, gauze, ace bandage, antiseptic, tweezers, scissors, cotton-tipped applicators)
  - moleskin for blisters
  - aloe gel for sunburns
  - digital thermometer
  - oral rehydration solution packets
- Health insurance details, an copies of same, and copies of claim forms

Other items that may be useful in certain circumstances
- Mild sedative or other sleep aid
- Medication to prevent altitude sickness
- Water purification tablets
- Commercial suture/syringe kits to be used by local health-care provider. (These items will also require a letter on letterhead stationery from the prescribing physician.)
- Personal protective contraception measures

NOTE: There are certain medications that are banned by the World Anti-Doping Agency (WADA). Before administering them, for valid medical indications, the medical professional needs to determine their legality and the athlete needs to be fully informed of any possible consequences. WADA and the athlete's sport management body may also need to be informed. A record of all medications administered needs to be up to date and maintained.
Source: adapted from Milne, 1996; Shaw and Dallimore, 2005; Whatley and Barbeau, 2010 [8–10].

that a flight crosses [14]. The symptoms of jet leg include an inability to sleep at the correct local time, irritability, depression, difficulty concentrating, disorientation, loss of appetite and gastrointestinal disturbances [16, 19]. Also, it is recognised that travel in an easterly direction produces greater jet lag because it compresses the 24-hour day and creates more physiological stress [17, 20]. Hence, the number of time zones crossed is considered the major underlying cause of jet lag and the desynchrony of an athlete's natural circadian rhythm [3].

A general rule regarding the rate of adjustment for jet lag recommends a 1-day adjustment per time zone crossed. Moreover, any strategy designed to counter the effects of jet lag should include a behavioural and pharmacologic approach [16]. Behavioural strategies involve avoiding sleep deprivation prior to travel, slowly adjusting sleep schedules toward the local time schedule at the competition destination, and selecting flight schedules allowing the least time passage between arriving at the destination and sleeping for a full night [3, 19]. Regular fluids in-flight to maintain hydration, and avoiding alcohol and caffeine is also recommended.

Various pharmacologic strategies have been utilised to reduce the effects of jet lag. Amphetamines, modafinil and pemoline, all drugs that increase alertness and mental performance over extended periods without sleep, should be avoided by athletes because they are banned by the International Olympic Committee and the World Anti-Doping Agency [16]. Soporific (hypnotic) drugs, a class of psychoactives used to induce sleep, can be useful to travelling athletes. Among these drugs are benzodiazepines such as diazepam (valium), loprazolam and zolpidem, as well as non-benzodiazepines such as zopiclone and zaleplon. Diazepam may be unsuitable because of residual effects on alertness and psychomotor performance, and loprazolam can inhibit physical performance up to 10 hours after administration [16, 21]. Melatonin, a hormone synthesised from serotonin, has been shown to alleviate jet lag when a dose of 3–5 mg is taken at bedtime on the first evening of arrival and continued for 5 days [16, 20]. Melatonin has no hangover effects on athlete performance the next morning [22].

Athlete villages

On arrival at major international sporting events, many athletes lodge at athlete villages such as the famed Olympic villages. While most athlete villages are conveniently located within the vicinity of their sport venues, athletes should be prepared for the challenges of being housed with numerous other athletes in close conditions. Noise from partying athletes who have completed their competitions and noise from surrounding urban areas can prove problematic [16]. Likewise, athletes should be prepared for dealing with unfamiliar bedding, event transportation schedules and congested traffic, media operations and the distraction of other athletes.

The sexual health of the athletes

Rapid global economic growth has been paralleled by a sexual revolution that has seen rates of sexually transmitted infections increase dramatically. Travel is often associated with loosening of inhibitions, a sense of anonymity and splitting of fixed sexual partnerships. All of these factors increase the likelihood of casual sexual liaison [23]. A Swiss study of people attending a travel clinic revealed that 51% of travellers reported casual sex abroad and 38% of the contacts were unprotected [24]. Thus, travelling athletes need to be advised about the significant risks associated with unprotected casual sexual relations.

Following a successful sporting venture, there is evidence that physical fitness correlates with better sexual function [25]. Add the risk factor of alcohol to the 'mix' of athletes and their sexual behaviour, and sexual risk-taking increases [26]. This is particularly significant for females and suggests that heavy episodic drinking (HED) plays a relatively more important role in sexual risk-taking among female athletes than among their male peers [26]. Of particular interest to athletes is that alcohol use, especially HED, has also been documented in numerous studies related to unplanned or unprotected sex and having multiple sex partners. With HED, while both male and female athletes reported elevated sexual risk behaviours compared with their non-drinking peers, the effect of HED on sexual risk-taking was twice as large in females as in males.

Blood-borne and sexually transmitted infections such as human immunodeficiency virus (HIV) and hepatitis B virus (HBV) continue to remain major global health problems [27]. The World Health Organization (WHO) reports that there are around 33 million individuals with HIV globally [28]. Another 2 billion people worldwide having been infected with HBV, of whom 350 million live with chronic infection [29]. While the risk of transmission during a contact sport is low, with a range from one transmission in 10,000–4.25 million games for HBV and one transmission in 43 million games for HIV, prevention measures are easily taught and need to be conveyed to all athletes.

It should be pointed out that there is no definite evidence that transmission of blood-borne infections among athletes through sexual activity is more common than for the general population [27]. However, some studies have suggested that some high-risk sexual activities may be more common among male athletes than non-athletes, and that athletes

may engage in more sexual activity, practise less safe sex, have a greater prevalence of sexually transmitted diseases and have a greater number of sexual partners [26, 30]. Nevertheless, others have made a valid case for the reverse: that sexual activity is not enhanced by sporting activities and athleticism [31, 32]. Despite all the academic data available on this topic, the myth of athlete and sexual prowess remains intact and was recently promulgated by comments from those who competed at the Beijing Olympics. Headlines such as 'Final weekend in Beijing set to be a sex fest!', followed up with this comment: 'As the Olympic Games draw to a close, the athletes in Beijing are reportedly preparing to go wild for an all-out sex weekend in the Olympic village', did much to promote the image of athletes as being raunchy and promiscuous [33].

Infectious diseases and sports travel

Athletic competition, athletic training and travel for sporting events create abundant opportunities for the spread of infectious disease. Disease outbreaks among athletes have been documented for decades, at least as far back as several outbreaks of Trachoma among wrestlers in the 1920s and 1930s [34, 35]. In the ensuing decades, travel to athletic competitions has expanded and this has increased the risks and opportunities for the spread of mundane and exotic infections. Not surprisingly, documentation of infectious disease outbreaks among travelling athletes has revealed that different patterns of disease apply to team sports, contact sports, adventure travellers and specific individual sports. In addition, it is not only the athletes who are at risk, but also their coaches, trainers, support staff, spectators and, at times, the local community. Athletes in particular are often at higher risk for infectious disease outbreaks because they may share personal items, live in close quarters while travelling, and may also participate in high-risk extra-curricular activities including unsafe sex, alcohol and illicit drugs, tattooing and the use of anabolic steroids [30, 36]. Since infectious disease outbreaks can be disastrous for an athlete or a team's ability to compete at a high level as well as posing a significant public health threat, it is important to understand the patterns of disease and the preventive and control measures that can be applied.

Issues related to team sports

Several diseases have been repeatedly documented among football players, rugby players, boxers, wrestlers and other school, collegiate and professional teams. These include herpes simplex, tinea infections, methicillin-resistant *Staphylococcus aureus* (MRSA), influenza, hepatitis B, measles, influenza and food poisoning. Contact sports such as rugby, wrestling and boxing provide excellent conditions for the spread of skin infections such as herpes simplex and tinea corporis. Herpes simplex and tinea corporis are so common among wrestlers that they have been given the specific names of herpes gladiatorum and tinea gladiatorum [37, 38].

Herpes gladiatorum

Herpes gladiatorum outbreaks consist of typical herpetic blisters on the face, neck, arm or shoulder. It spreads by direct skin-to-skin contact and has a probability of transmission of up to 47% if herpes simplex develops on a sparring partner [37]. Open wounds and abrasions increase the risk of transmission.

Prevention

- Screening participants for active lesions and not allowing infected athletes to compete.
- Varying guidelines exist but the recommended exclusion time is a minimum of 120 hours (5 full days) of oral antiviral treatment, no new lesions and all prior lesions crusted over.
- Covering active lesions is not sufficient.
- Antiviral prophylaxis with acyclovir, valaciclovir or famciclovir to reduce the risk of recurrence and transmission among athletes known to be affected.
- In some cases, antiviral prophylaxis of the entire team is undertaken for the duration of the season.
- Avoid sharing of soap, towels, gear and other personal items.

Tinea gladiatorum

Tinea gladiatorum outbreaks are usually due to *Trichophyton tonsurans*. Lesions can be atypical without the typical annular appearance of tinea corporis ('ringworm'), and are commonly found on the head, neck and arms. Transmission is primarily via direct skin-to-skin contact.

Prevention

- Screening and exclusion of affected athletes.
- Prompt treatment of affected athletes, preferably with oral antifungals.
- Covering of focal lesions may be permissible.
- Attention to hygiene.
- Avoidance of sharing wrestling headgear.

Community-acquired methicillin-resistant *S. aureus*

Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) has been described since the early 1980s. In recent years it has been increasingly linked with sports such as

football, basketball, rugby, wrestling, volleyball, fencing, cross-country running and among river rafting guides [38–40]. Lesions are cutaneous and can range from minor furuncles to necrotising fasciitis requiring hospitalisation and surgery. Risk factors include frequent antibiotic use, compromised skin barriers, skin contact between players, inadequate hygiene and shared personal items.

Prevention
- Covering all wounds.
- Excluding any athletes with lesions that cannot be adequately covered.
- Encourage good hygiene.
- Avoid sharing towels and personal items.
- Regular cleaning of shared equipment.
- Provide disposable paper towels and alcohol-based hand sanitizers.
- Keep finger nails and toe nails short.
- Avoid wearing jewelry to prevent scratches.
- In some cases, nasal decolonisation with mupirocin may be helpful.

Measles

Measles is one of the mostly highly contagious infectious diseases and spread primarily by airborne transmission. Hence, this makes it an important risk at international sporting events and events taking place in domed stadiums. A particularly well-known measles outbreak occurred in conjunction with the International Special Olympics Games in July 1991. Twenty-five cases were tracked back to a primary case in a track and field athlete from Argentina; some of the cases were among spectators [41]. A number of other outbreaks have been reported in domed stadiums [40, 42, 43].

Prevention
- Vaccination of susceptible individuals.
- Rapid reporting and isolation of any reported cases.
- Prophylactic vaccination of individuals exposed to measles can provide protection if given within 72 hours of exposure.

Blood-borne infections

Although there is a theoretical risk of HIV transmission during contact sports via contact with open cuts and abrasions with infected blood, no confirmed case associated with sports has occurred. Blood doping and drug abuse do, however, pose a significant risk for transmission of HIV, as well as hepatitis B and C. There have been reports of transmission of all these viruses by the sharing of needles to inject anabolic steroids or vitamins [36, 43–47]. Hepatitis B has a risk for transmission 50–100 times higher than transmission of HIV and is a significant risk in contact sports [27]. Moreover, hepatitis B virus (HBV) can be stable on environmental surfaces for at least 7 days and is resistant to drying, simple detergents and alcohol. The infectivity of the disease is evidenced by the example of a well-documented outbreak of hepatitis B that was reported in a high school sumo wrestling club [48]. In another incident, 11 members of an American football team at a university in Japan contracted hepatitis B as a result of contact with open wounds while practising [49].

As routine hepatitis B vaccination is becoming common, the risks of hepatitis B transmission may become less important over time. However, at the present time, significant risk still exists, especially in the context of international travel to regions that remain highly endemic for hepatitis B.

Prevention
- Prompt and appropriate treatment of bleeding sports injuries, using gloves and proper equipment.
- Removing athletes with bleeding injury from the event as soon as possible.
- Prompt changing of blood-soaked uniforms and equipment (with immediate removal from the sports activity area).
- Any skin injuries should be covered with an occlusive dressing during sports activities.
- All wounds and injuries should be promptly reported and dealt with.
- Appropriate protective measures in contact sports.
- Some athletic organisations require HIV testing.

The hepatitis B vaccine is safe and 95% effective. Many countries now integrate hepatitis B vaccination into their routine childhood immunisation schedules. As a minimum precaution, the following should receive hepatitis B vaccine:
- participants in contact and collision sports such as wrestling and boxing
- athletes who travel regularly to regions of high endemicity
- athletes living in regions with endemic hepatitis B
- athletes suspected of doping
- athletes who practise first aid
- those with other risk factors.

Enteroviral and meningococcal meningitis

In the summer of 1997, an outbreak of meningococcal meningitis occurred following an international youth football tournament, affecting individuals from four European countries [50]. Several outbreaks of aseptic meningitis have also been reported in team sports [51, 52]. Living in close

quarters such as dormitories is a known risk factor for meningitis. In addition, outbreaks can occur via transmission through the sharing of water bottles or by drinking water from contaminated water coolers.

Prevention
- Vaccination against meningococcal meningitis may be recommended for high school and college athletes.
- Rapid identification of cases and chemoprophylaxis of contacts of meningococcal meningitis.
- Avoid sharing of water bottles.

Gastrointestinal infections

Transmission of gastrointestinal infections can occur during athletic competition. In one well-known case, an outbreak of Norovirus occurred among the football team and staff of the University of North Carolina, starting with turkey sandwiches from a catered lunch box. Fifty-four out of 108 players and staff became ill. In addition, 11 players on the opposing team from the University of Florida also became ill despite not eating the sandwiches [53]. Furthermore, travelling for sports participation exposes athletes to all the risks of traveller's diarrhoea, food poisoning and parasitic infections such as *Giardia lamblia* and *Entamoeba histolytica*. Infections can spread rapidly among team members or common-source transmission can affect many members within a short period of time. In either case, the effects on the competition can be very significant. Moreover, as noted above in the case of the University of North Carolina football plays, it can also spread to players on opposing teams.

Prevention When travelling for sports, particularly to less developed countries, athletes and staff should follow the well-established guidelines for food safety while travelling.
- Avoid drinking tap water, non-carbonated bottled water, unpasteurised milk or iced drinks.
- Avoid raw vegetables and fruits that cannot be peeled.
- Be very careful of seafood and never eat uncooked seafood (such as oysters).
- Only eat food served piping hot.
- Avoid food that requires elaborate preparation.
- In some cases, chemoprophylaxis (generally with ciprofloxacin or azithromycin) may be considered to reduce the risk of gastroenteritis from food-borne pathogens [54].

Influenza

Influenza is one of the most frequently identified illnesses among travellers, and mass gatherings such as sporting events may increase the likelihood of transmission. At the time of writing, a significant global outbreak of pandemic influenza H1N1 was underway and sporting events such as the Olympics pose a significant risk for mass infection.

Prevention
- Vaccination of athletes and staff prior to travel.
- Prompt identification and isolation of cases, with early treatment with oseltamavir or zanamavir.
- Oseltamavir prophylaxis for unvaccinated close contacts of cases.

Issues related to adventure sports

In September of 2000, several cases of an unusual febrile illness were identified through the GeoSentinel Surveillance Network in participants in the Eco-Challenge-Sabah 2000 multisport endurance race held in Malaysian Borneo. Three hundred and four athletes from 26 countries participated in the race, which involved jungle trekking, swimming and kayaking (in both fresh and ocean water), spelunking, climbing and mountain biking. After the event, more than 20 athletes were confirmed to have contracted leptospirosis as the result of exposure to water from the Segama River. Athletes who had used doxycycline for malaria prophylaxis appeared to be somewhat protected [55]. This episode highlights how adventure sports and international travel can coincide to pose unique and little-known risks to athletes. Other waterborne pathogens that are potential risks include schistosomiasis, giardia and some enteric infections. Specific activities such as river rafting may also be a risk factor for staphylococcal skin infections [56]. Furthermore, in addition to waterborne issues, adventure sports can also expose athletes to ticks and rickettsioses, malaria and other mosquito-borne illnesses such as Japanese encephalitis, yellow fever and West Nile virus. In some locations, adventure athletes may run the risk of exposure to rabies, for example, during competitions involving spelunking. For adventure athletes involved in long-distance running, it should be noted that they are at an increased risk for upper respiratory tract infections. This is especially true for runners who run in excess of 96 km a week [57].

Prevention
- Use appropriate protective gear.
- Insect repellent (this may even be somewhat protective against waterborne illnesses).
- Consider prophylaxis with doxycycline 200 mg weekly for participants in multisport activities where risk of leptospirosis via fresh water exposure exists.
- Malaria prophylaxis should be offered as appropriate to the destination. Where malaria prophylaxis is required, doxycycline may be preferable because of its added protection against leptospirosis and rickettsial diseases.

• Consider rabies pre-exposure vaccination for athletes who may have significant likelihood of exposure to rabies risk (for example spelunkers, cyclists in some countries), particularly when travelling to destinations where post-exposure rabies treatment may not be fully available. At a minimum, athletes and support staff should be educated about the care of animal bites and the nearest availability of appropriate post-exposure rabies prophylaxis.
• Vaccinate appropriately against yellow fever and Japanese encephalitis, depending on destination.
• Athletes should maintain good nutrition, avoid overtraining and get adequate rest. Influenza vaccination is advisable.

Other potential sports travel-related infections not mentioned above include verrucae, chickenpox, otitis externa, vibrio (cholera) and other food poisoning, typhoid, schistosomiasis, Legionnaires' disease, tetanus, dengue fever, Japanese encephalitis, malaria, TB, pertussis and Ebola/Marburg.

Vaccine-preventable disease

Prior to departing for athletic competitions, it is recommend that all athletes have up-to-date vaccination against:
• tetanus
• diphtheria
• whooping cough
• polio
• measles, mumps and rubella
• influenza
• varicella.

Additional vaccinations should be considered on a destination and sports-specific basis and should take into account length of travel and likely exposures.
• Hepatitis A – Immunisation is recommended for most travellers.
• Typhoid – Immunisation is recommended for most travellers, particularly to Asia, sub-Saharan Africa or south or central America.
• Hepatitis B – Immunisation is recommended for all athletes competing in contact sports where exposure to blood is a possibility. All wrestlers and boxers should be immunised. It is also recommended for anyone who might have sexual exposure or be at risk through other behaviours.
• Pneumococcal vaccination – should be advised for all athletes with cardiorespiratory conditions including asthma, and for any athlete who smokes.
• Meningococcal meningitis – Immunisation is recommended for all high school and collegiate teams prior to travel, and for travellers to the meningitis belt of Africa. The quadrivalent (ACWY) vaccine is generally recommended, to provide maximum coverage.
• Rabies – Immunisation is recommended for athletes who will have extensive outdoor exposure in rural areas, and for all cavers or spelunkers. Availability of post-exposure rabies treatment should be considered and a low threshold for vaccination should be maintained for athletes travelling to areas where rabies is endemic in animals.
• Yellow fever – Immunisation is required for athletes travelling to yellow fever zones in Africa and South America
• Japanese encephalitis – Immunisation should be considered for athletes who will have extensive outdoor exposure in areas of Asia where Japanese encephalitis is a risk. The new two-dose killed vaccine has an excellent safety and immunogenicity profile and has lowered the threshold for vaccination.
• Tick-borne encephalitis – Immunisation should be considered for athletes who will have extensive outdoor exposure in areas of Europe where TBE is a risk.

It is important to note that immunisations should be planned several months in advance to allow adequate time to administer the required number of doses. Dukoral can be considered for some temporary protection against Traveller's Diarrhoea.

Malaria

Malaria should never be forgotten in the athlete's pre-travel assessment or when an athlete presents with fever after travel. Standard malaria prevention guidelines should apply and are somewhat destination specific. The side effects of preventive medications may be particularly significant for athletes and should be considered when choosing which medication to prescribe. For example, doxycycline may cause sun sensitivity and gastrointestinal upset, which may make it inappropriate for some athletes. On the other hand, it provides protection against other travel-related illness such as leptospirosis and some rickettsioses and this may make it a good choice in athletes known to tolerate it well. Mefloquine may be an undesirable antimalarial in those with a history of mental illness.

Decisions about prophylaxis should therefore take into account:
• official recommendations about the destination
• the length of travel
• the athlete's medical history
• the athlete's previous experience with antimalarials
• the side-effect profile of the medications.

In addition, insect bite preventive measures should be aggressively applied. The malaria-causing anopheles mosquitoes are night-biters, but other disease causing mosquitoes are day-biting.

Athlete safety and security

Motor vehicle crashes have consistently been identified as the most frequent cause of injury death for tourists[20, 58, 59]. If renting a motor vehicle or acting as the primary driver, athletes should familiarise themselves with the driving rules and the driving etiquette of their destination country [3]. Also, if renting a motor vehicle, care should be taken to ensure that the vehicles are roadworthy, with proper working equipment such as headlights, seatbelts, brakes, signal lights and a spare tyre [6]. If driving in winter conditions, athletes should ensure there is winter tread on the tyres, functioning wiper blades, and be aware of driving techniques such as keeping extra distance between vehicles and expecting icy conditions around intersections [20].

Since athletes are heavily focused on their competition, it is easy for them to forget the criminal aspects of international travel. Yet, with events such as the 1972 Munich Olympics massacre, the 1996 Atlanta Olympic Park bombing, the 1993 stabbing of tennis star Monica Seles, and the ever-present threat of terrorism, hooliganism and fan violence near sport venues, security should always be a priority for athletes [60, 61]. The overall security at large public events such as the Olympic Games has improved over the past three decades but the prospect of crimes against individual athletes or national teams still exists [16]. To prevent such incidents from occurring, athletes need to understand the potential for political violence against them or their team and be sure to employ the same travel advice provided to tourists. For example, athletes should seek out local destination advice when visiting for competition and avoid going into areas with high crime reputations [6]. When possible, athletes should try and avoid travelling alone or carrying large amounts of cash with them in public, and should make an effort to stay in lodgings with secure reputations. It would also assist athletes if they made multiple copies of all documentation and identification, plan for emergency finances and have access to two days of spare funding, purchase travel insurance, and leave a detailed copy of their itinerary and all contact information with family or contacts at home.

Post-competition activities

At the conclusion of competition, the same procedures and strategy for travel to the sporting event should be reviewed by athletes and their support staff. Any athletes injured during travel or competition should be monitored during the trip home [3]. On arrival at home, there should be a formal debriefing session to allow any lessons learned to be disseminated in order to aid the planning for future events [7]. Each report on sustained injuries should include a final disposition, diagnosis and definitive treatment [62]. In addition, a surveillance system to monitor any injury or illness not evident during the competition should be instituted. Medical supplies will also need to be inventoried, restocked and returned to their storage area.

References

1. Young M *et al.* (1998) The traveling athlete: issues relating to the Commonwealth Games, Malaysia, 1998. *Clin J Sports Med* **8**: 130–135.
2. Hadjichristodooulou C *et al.* (2005) Mass gathering preparedness: the experience of the Athens 2004 Olympic and Para-Olympic Games. *J Environ Hlth*: **67**, 42–57.
3. Kary JM and Lavallee M (2007) Travel medicine and the international athlete. *Clin Sports Med* **26**: 489–503.
4. Shaw M and Leggat P (2000) Traveling to Australia for the Sydney 2000 Olympic and Paralympic Games. *J Travel Med* **7**: 200–204.
5. Leggat PA and Shaw MTM (2003) From Sydney to Athens: preparing for the Olympic and Paralympic Games. *Travel Med Infect Dis* **1**: 201–203.
6. Shaw M *et al.* (2007) Travelling to China for the Beijing 2008 Olympic and Paralympic Games. *Travel Med Infect Dis* **5**: 365–373.
7. Milne C *et al.* (1999) Medical issues relating to the Sydney Olympic Games. *Sports Med* **28**: 287–298.
8. Milne CJ (1996) The pocket sports doctor. Dunedin, Sports Medicine New Zealand.
9. Shaw MTM and Dallimore J (2005) The medical preparation of expeditions: the role of the Medical Officer. *Travel Med Infect Dis* **3**: 213–223.
10. Whatley AD and Barbeau DN (2010) Travel Health Kits. Travelers' Health: Yellow Book 2010, http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/travel-health-kits.aspx (accessed 9 February 2010).
11. Waterhouse J *et al.* (2004) The stress of travel. *J Sports Sci* **22**: 946–965.
12. Ansari M *et al.* (2005) Traveler's thrombosis: a systematic review. *J Travel Med* **12**: 142–154.
13. Reilly T *et al.* (2005) Jet lag and air travel: implications for performance. *Clin Sports Med* **24**: 367–380.
14. Hovens M *et al.* (2006) Aspirin in the prevention and treatment of venous thromboembolism. *J Thromb Haem* **4**: 1470–1475.
15. Flower D (2004) Commentary. *J Sports Sci* **22**: 965–966.
16. Milne CJ and Shaw M (2008) Travelling to China for the Beijing 2008 Olympic Games. *Br J Sports Med* **42**: 321–326.
17. Auger RR and Morgenthaler TI (2009) Jet lag and other sleep disorders relevant to the traveler. *Travel Med Infect Dis* **7**: 60–68.
18. Silverman D and Gendreau M (2009) Medical issues associated with commercial flights. *Lancet* **373**(9680): 2067–2077.
19. Manfredini R *et al.* (1998) Circadian rhythms, athletic performance, and jet lag. *Br J Sports Med* **32**: 101–106.

20. Heggie TW (2009) Traveling to the Canada for the Vancouver 2010 Winter Olympic and Paralympic Games. *Travel Med Infect Dis* **7**: 207–211.
21. Grobler LA *et al.* (2000) Comparative effects of zopiclone and loprazolam on psychomotor and physical performance in active individuals. *Clin J Sports Med* **10**: 123–128.
22. Atkinson G *et al.* (2001) Are there hang-over effects on physical performance when melatonin is ingested by athletes before nocturnal sleep? *Int J Sports Med* **22**: 232–234.
23. Matteelli A and Carosi G (2001) Sexually transmitted diseases in travellers. *Clin Infect Dis* **32**: 1063–1067.
24. Gagneux OP *et al.* (1996) Malaria and casual sex: what travelers know and how they behave. *J Travel Med* **3**: 14–21.
25. Karatas OF *et al.* (2009) The evaluation of clitoral blood flow and sexual function in elite female athletes. *J Sex Med* **7**: 1185–1189. doi: 10.1111/j.1743- 6109.2009.01569.x
26. Huang J-H *et al.* (2009) Sexual risk-taking behaviors, gambling, and heavy drinking among US college athletes. *Arch Sex Behav* **2010**: 706–713. doi: 10.1007/s10508-009-9521-7
27. Kordi R and Wallace WA (2004) Blood borne infections in sport; risks of transmission, prevention, and recommendations for hepatitis B vaccination. *Br J Sports Med* **38**: 678–684.
28. World Health Organization (2009) New HIV Infections Reduced by 17% over the Past Eight Years, http://www.who.int/mediacentre/en/ (accessed 3 February 2010).
29. World Health Organization (2008) Hepatitis B, http://www.who.int/topics/hepatitis/en/ (accessed 6 February 2010).
30. Nattiv A *et al.* (1997) Lifestyles and health risks of collegiate athletes: a multicenter study. *Clin J Sports Med* **7**: 262–272.
31. Pate RR *et al.* (2000) Sports participation and health-related behaviors among US youth. *Arch Pediat Adol Med* **154**: 904–911.
32. Kulig K *et al.* (2003) Sexual activity and substance use among adolescents by category of physical activity plus team sports participation. *Arch Pediat Adol Med* **157**: 905–912.
33. Anonymous (2008) The Climax to the Olympic Games, http://www.bild.de/BILD/news/bild-english/sport-news/olympics-2008/08/22/olympic- sex-fest/on-the-final-weekend-in-beijing.html (accessed 3 February 2010).
34. Patton JM (1922) Wrestlers trachoma. *Am J Ophthalmol* **5**: 545.
35. Zentmayer W (1934) Trachoma in wrestlers. *Arch Ophthamol* **12**: 234–235.
36. Rich JD *et al.* (1999) The infectious complications of anabolic-androgenic steroid injection. *Int J Sports Med* **20**: 563–566.
37. Anderson BJ (2003) The epidemiology and clinical analysis of several outbreaks of herpes gladiatorum. *Med Sci Sports Exercise* **35**: 1809–1814.
38. Adams BB (2002) Tinea corporis gladiatorum. *J Am Acad Dermatol* **47**: 286–290.
39. Turbeville SD *et al.* (2006) Infectious disease outbreaks in competitive sports: a review of the literature. *Am J Sports Med* **211**: 1860–1865.
40. Kirkland EB and Adams BB (2008) Methicillin-resistant Staphylococcus aureus and athletes. *J Am Acad Dermatol* **59**: 494–502.
41. Ehresmann KR (1995) An outbreak of measles at an international sporting event with airborne transmission in a domed stadium. *J Infect Dis* **171**: 679–683.
42. Centers for Disease Control and Prevention (CDC) (1992) Measles at an international gymnastics competition: Indiana. *MMWR: Morbid Mortal Wkly Rep* **41**: 109–111.
43. David RM *et al.* (1987) A persistent outbreak of measles despite appropriate prevention and control measures. *Am J Epidemiol* **126**: 438–449.
44. Henrion R *et al.* (1992) HIV contamination after infections of anabolic steroids. *Presse Medicale (Paris, France: 1983)* **8**: 218.
45. Sklarek HM *et al.* (1984) AIDS in a bodybuilder using anabolic steroids. *New Engl J Med* **311**: 1701.
46. Scott MJ and Scott MJJ (1989) HIV infection associated with injections of anabolic steroids. *JAMA: J Am Med Assoc* **14**: 207–208.
47. Parano R *et al.* (1999) Intravenous vitamin complexes used in sporting activities and transmission of HCV in Brazil. *Am J Gastroenterol* **94**: 857–858.
48. Kashiwagi S *et al.* (1982) An outbreak of hepatitis B in members of a high school sumo wrestling club. *JAMA: J Am Med Assoc* **248**: 213–214.
49. Tobe K *et al.* (2000) Horizontal transmission of hepatitis B virus among players of an American football team. *Arch Intern Med* **160**: 2541–2545.
50. Reintjes R *et al.* (2002) Detection and response to a meningococcal disease outbreak following a youth football tournament with teams from four European countries. *Int J Hyg Environ Hlth* **205**: 291–296.
51. Baron RC *et al.* (1982) Aseptic meningitis among members of a high school football team: an outbreak associated with echovirus 16 infection. *JAMA: J Am Med Assoc* **1248**: 1724–1727.
52. Alexander JP *et al.* (1993) Coxsackie B2 infection and aseptic meningitis: a focal outbreak among members of a high school football team. *J Infect Dis* **167**: 1201–1205.
53. Kilgore PE *et al.* (2000) A university outbreak of gastroenteritis due to a small round-structured virus application of molecular diagnostics to identify the etiologic agent and patterns of transmission. *J Infect Dis* **181**: 1467–1470.
54. Karageanes SJ (2007) Gastrointestinal infections in the athlete. *Clin Sports Med* **26**: 133–148.
55. Sejvar J *et al.* (2003) Leptospirosis in eco-challenge athletes, Malysian Borneo, 2000. *Emerg Infect Dis* **9**: 702–707.
56. Decker MD *et al.* (1986) An outbreak of staphylococcal skin infections among river rafting guides. *Am J Epidemiol* **124**: 969–976.
57. Nieman DC (1996) The immune response to prolonged cardiorespiratory exercise. *Am J Sports Med* **24**: S98–103.
58. Wilks J (1999) International tourists, motor vehicles and road safety: a review of the literature leading up to the Sydney 2000 Olympics. *J Travel Med* **6**: 115–121.
59. Heggie TW *et al.* (2008) Recreational travel fatalities in US National Parks. *J Travel Med* **15**: 404–411.
60. Madzimbamuto FD (2003) A hospital response to a soccer stadium stampede in Zimbabwe. *Emerg Med J* **20**: 556–569.
61. Yancey AH *et al.* (2008) World Cup 2010 planning: an integration of public health and medical systems. *Public Health* **122**: 1020–1029.
62. Burdick T (2005) Wilderness event medicine: planning for mass gatherings in remote areas. *Travel Med Infect Dis* **3**: 249–258.

Chapter 35 Space tourism – the future in travel health?

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Introduction

The study of human life and performance at physical extremes defines the narrow physical envelope that is able to support human life. For humans without protective pressure garments, breathing gas mixtures equivalent to room air, comprising approximately 21% oxygen and 79% nitrogen, this envelope extends a few kilometres above the sea level and to only a few tens of metres when submerged. The lessons learnt from studies in mountain, polar, desert and subaqua environments suggests simply that humans may persist at these extremes but not indefinitely and not without penalty.

The space environment lies beyond this envelope of human survival, and does not support life for any period of time. Characterised by microgravity, hard vacuum, radiation and thermal extremes no acclimatisation is possible and instead human explorers of space must rely on artificially engineered systems for their protection and survival.

For 40 years following Yuri Gagarin's first orbital space flight, only professional crews, engaged in programmes of space exploration on behalf of international agencies, took part in human space flight. However, in 2001 millionaire Denis Tito became the first commercial passenger to fly into space. Tito was launched aboard a Soyuz capsule on a mission which lasted nine days and included a short stay aboard the international space station. This event ushered in the age space tourism. To date, seven people have paid for seats aboard Russian Soyuz vehicles and flown to the International Space Station. This development, along with the imminent advent of suborbital flights, represents a shift in the human space flight paradigm.

Space medicine

The discipline of space medicine has, until now, been almost exclusively dedicated to the support of programmes of exploration, prosecuted by international space agencies and crews of professional astronauts. These activities rely heavily on strategies of preventive medicine with many appropriately qualified candidates disqualified at the outset for failing to meet strict medical requirements. As such, the medical risks of space flight and exposure to the space environment are in large part mitigated and the probability of in-flight medical events greatly reduced.

However, we approach the dawn of a new era, one in which private individuals will more regularly and more frequently experience episodes of space flight as fee-paying passengers. In sharp contrast to professional astronaut corps selection processes, neither commercial space flight operators nor potential space tourists will consider medical conditions a reason for automatic disqualification from space flight.

If commercial space flight operations flourish, one can expect a wide variety of mission profiles of different durations, flight and acceleration profiles. The age of suborbital space tourism is reportedly imminent, but there are already proposals for commercial low-Earth orbit hotel operations, orbital flights and even circumlunar tours. Should these ambitions be realised this era will require a new approach to space medical operations. And while suborbital flight profiles are short in duration, commercial spacelines will more than likely have to accept some responsibility for the health of space participants in the pre-flight and post-flight period. Should the ambitions of commercial space flight operators be fully realised this will represent a new paradigm in human space flight operations and will demand a new approach to space medicine.

The field of space medicine has historically drawn on expertise from a vast spectrum of subspecialities, from occupational medicine to orthopaedic surgery. In the future, as the population flying in space becomes more heterogeneous in terms of age and health, a still broader range of expertise will be required.

This chapter discusses some of the challenges facing physicians responsible for qualifying space participants for flight,

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outlines existing solutions where they exist and speculates about countermeasures that may facilitate future programmes of space tourism.

Definitions

The space flight participant

Some controversy exists over how best to refer to private citizens who purchase space flight opportunities through commercial providers. The Fédération Aéronautique Internationale (FAI) convention dictates that the title of astronaut be conferred on all those who achieve an altitude of more than 100 km, no matter what their role within that flight. The United States operate to different standards, conferring astronaut wings on all those achieving 80 km or more, a definition that allows all eight, suborbital X-15 pilots to qualify.

The term space tourist is seen in some quarters almost as a pejorative term. Currently, those travelling under commercial agreements on space vehicles are not a substantive element of exploration missions. However, for Soyuz vehicles the space tourist must undergo a similar training regimen to professional astronauts and must be fully versed in emergency procedures. In view of this it is regarded by some as inappropriate to refer to commercial passengers merely as tourists and the term 'space participant' or 'commercial astronaut' is sometimes preferred.

The predominant risk to the health of those who fly in space is, and may for some time continue to be, that of failure of complex aerospace engineering systems. It is worth noting that, in more than half a century of space flight there have been 18 fatalities in-flight, all of which are attributable to failure of the vehicle or its environmental control and life support systems. These risks are accepted by all who choose to fly aboard high performance, super and hypersonic vehicles. The risks of catastrophic vehicle failure currently continue to dominate human space flight activities and these risks cannot be mitigated by programmes of space medicine.

If programmes of space tourism are to flourish, the reliability of space vehicles and their launchers will have to far outstrip that of existing human space flight systems. Suborbital flights, which can reach the space flight boundary at lower velocities and which do not achieve orbit, are substantially less energetic than their orbital counterparts. And though formidable challenges remain in the engineering of such vehicles, the reduction in velocity and energy associated with these less demanding flight profiles may contribute to greater flight safety.

The space environment

The space flight environment is uniquely hostile to human physiology.

Space flight boundaries

The following boundaries define altitudes significant in space travel (Figure 35.1).

- Armstrong line: the altitude at which atmospheric pressure is so low that water boils at body temperature (0.062 atmospheres) – approximately 18.9–19.4 km.
- Von Karman line: 100 km (accepted by the Fédération Aéronautique Internationale as the boundary between Earth's atmosphere and outer space. This is the altitude where the air is too thin for aeronautical purposes as any vehicle would have to travel faster than orbital velocity in order to derive sufficient aerodynamic lift from the atmosphere to support itself).
- Low Earth orbit: this is an orbit within the locus extending from the Earth's surface up to 2,000 km.
- True space.

Suborbital flight

Suborbital space flight refers to those in which altitudes of more than (100 km) are exceeded but in which the passenger craft itself does not acquire sufficient altitude or velocity to achieve Earth orbit. These flight profiles require that vehicles acquire low single-figure multiples of the speed of sound. The acceleration profile associated with these flights may nevertheless be relatively provocative both in terms of magnitude and rate of onset.

Orbital flight

Refers to vehicles that achieve sufficient energy and velocity to achieve Earth orbit. Most current orbital missions occur at low orbital inclinations at altitudes of around 400 km. It is worth pointing out that the increase in velocity required to attain low Earth orbit increases by an order of magnitude over that necessary for suborbital flight. Furthermore, since kinetic energy increases proportionally as the square of the velocity of vehicle, the energetic requirements are considerable.

Space station operations

The International Space Station is currently the only operational, orbiting space station available to human crews. The first modules of this space station were launched in 1998 and construction is due to be completed in 2011. Barring mishap

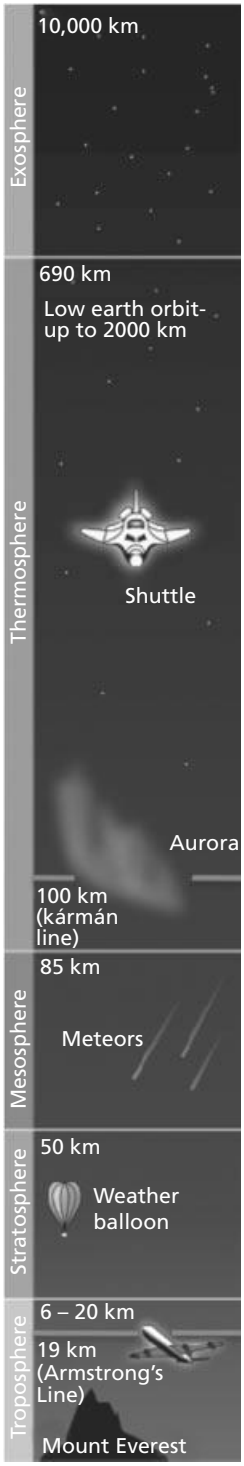

Figure 35.1 A figure demonstrating the layers of atmosphere (troposphere, stratosphere, mesosphere, thermosphere and exosphere, and Armstong and Von Karman's lines).

it is likely that this vehicle will remain operational until 2020. It has hosted all seven of the flown space tourists and there are plans for further tourist flights to this platform.

Circumlunar flights

At least one commercial company has proposed circumlunar flights for paying passengers – flights that would leave low Earth orbit and pass around the Moon in the same way as the Apollo 8 crew of 1968. Such missions, should they be realised, entail the added challenges of additional remoteness, close confinement, severely constrained medical capability and the inability to return to Earth at short notice should a medical contingency arise.

Microgravity

Microgravity refers to the state of near-total gravitational unloading experienced by objects and individuals during space flight. The gravitational fields generated by massive bodies such as the Earth, Moon and Sun, extend effectively for an infinite distance into space. It is thus impossible to escape the influence of gravity. The weightlessness experienced by astronauts is not due to the absence of gravity as the more colloquial term 'zero-G' might suggest. Astronauts in orbit around celestial bodies experience microgravity as a consequence of freefall. If an individual were to stand on a set of bathroom scales in a lift and then cut the supporting cable, both the lift, the scales and the person would fall freely, under the influence of gravity. The scales would register no weight since there would be no resultant force acting on the scales or astronaut (the person would be falling toward the scales as fast as the scales were falling away from him and hence no force could be applied by the person to the scales). The entire system would be weightless as a consequence of freefall.

Health problems of space travel

Significant acceleration force is required to achieve orbital and escape velocities. These degrees of acceleration, essentially leading to hypergravitational loads, are not normally experienced in everyday travel. The extremes of hypergravity and microgravity have an effect on human physiology with the potential to exacerbate existing medical problems and generate pathophysiological changes.

Acute risks

Table 35.1 list the risks inherent to all forms of space travel.

Table 35.1 The risks inherent to all forms of space travel

Acceleration
Space environment
– Radiation
– Hypobaria/Decompression sickness
– Thermal
Vehicle environment
– Confinement
– Toxic exposures
– Environmental control and life support
Vehicle dynamics
– Motion sickness
– Trauma on return to normal G/hyper G
– Acceleration

Acceleration

The crew of a space shuttle achieves an orbital velocity of around 17,000 miles per hour and experiences loads of up to 3G along the +Gx axis (i.e through the chest from anterior to posterior).

While passengers on suborbital flights achieve lower overall attitudes and velocities (typically low multiples of the speed of sound), they may experience higher G loads, with greater rates of onset, albeit for shorter periods of time. The effects of these forces are largely determined by the axis along which the accelerative force is experienced. In general, forces along the Gx axis are tolerated better than those along the Gz axis (i.e from head to toe).

While these forces are tolerated by the physiologically fit, they may not be by passengers with cardiac compromise, resulting in loss of consciousness. Much depends on the direction this force is applied through the body. It should also be remembered, that unlike crew, the passenger will not be required to perform any critical tasks while exposed to this; however, these forces must be considered when deciding if a passenger is fit to fly. Most vehicles are designed such that passengers experience the accelerative force in the +Gx axis. +Gz accelerations have the potential to impact on cardiovascular physiology. As such, one can expect this force to be well tolerated by healthy individuals.

However, large sustained Gx or Gz axis accelerations might present difficulties for patients with significantly impaired respiratory function since they interfere with both respiratory mechanics and gas exchange. Furthermore, sustained Gz axis accelerations are tolerated poorly and they lead to dependent pooling of blood, reduced venous return and increased cardiac work while reducing myocardial oxygen supply.

Shorter duration accelerations might prove problematic for those with underlying musculoskeletal problems. For example one might need to exercise greater caution if an individual with severe rheumatoid arthritis wished to participate in a flight.

Exposure to microgravity

Microgravity affects many physiological systems if prolonged (see below). Acutely, the commonest health problem is Space Adaptation Syndrome.

Space Adaptation Syndrome/ Space Motion Sickness

Space Adaptation Syndrome (SAS) or Space Motion Sickness (SMS) is a condition in which an astronaut develops nausea/vomiting after the recent arrival in microgravity. It appears to affect the majority of astronauts flying for the first time [1] and ranges from mild to severe, usually lasting 2–4 days. Its pathogenesis is thought to relate to the altered effects of microgravity on the vestibular system, though cranial fluid shifts may contribute (see below). SAS appears to be exacerbated where crew members are free to move around the cabin and was reportedly lower in incidence during earlier capsule missions when crew members were confined to their seats. This entity is, however, largely self-limiting and standard anti-emetic therapies have been employed with success in the space programme.

Effects on intracranial pressure

Direct intracranial pressure (ICP) measurement has not been performed in microgravity. It is hypothesised, however, that with the fluid shifts that occur (see below), ICP increases and this may contribute to Space Adaptation Syndrome and headache [2].

Headache

Headache is common, occurring in approximately 70% of astronauts who would not ordinarily suffer headache [3]. This may reflect a rise in ICP though there are obviously many causes of headache.

Table 35.2 lists common medical complaints with microgravity.

Health problems with prolonged travel

Chronic effects of microgravity

Long-duration exposure to microgravity appears to impact almost all physiological systems. The effects of weightlessness on the musculoskeletal (i.e the system of muscles and

Table 35.2 Common medical problems in space flight

Acute and problematic
– Nausea (?space adaptation syndrome/space motion sickness)
– Headache (cranial fluid shift)
– Constipation
– Anaemia
– Weight loss
– Back pain
– Confinement
Long term and insidious
– Cardiovascular deconditioning
– Muscle and bone loss
– Autonomic instability

bones), cardiovascular (i.e. the heart and associated blood vessels) and neurovestibular systems (i.e. the brain and peripheral systems involved in spatial orientation, motor control and postural control) have historically been identified as being of key importance in terms of their operational impact. However, unexpected disturbances, of systems less dependent on gravitational loading, have also been observed. These include alterations in the synthesis of new blood cells leading to anaemia, deficiencies of the immune system and endocrine alterations affecting the human body's production and regulation of hormones [4, 5].

The longest continuous mission in the history of human space flight was completed by cosmonaut Valeriy Vladimirovich Polyakov aboard the Mir Space Station on 22 March 1995. Spanning the Soyuz TM-18 and Soyuz TM-20 mission increments between 8 January 1994 and 22 March 1995, this sortie lasted 437 days, 17 hours, 58 minutes. This mission was, however, exceptional in type and the vast majority of experimental data derived from human space exploration exists for mission durations of less than 3 months. Future missions that plan to deliver human crews to and return them from the surface of Mars may be of durations in excess of 30 months. This is more than twice as long as Polykov's record-breaking deployment and two orders of magnitude greater in duration than current, typical missions.

To overcome the biomedical problems associated with these long-duration missions it is likely that cross-disciplinary work spanning the boundaries between engineering, physical science and life science will be necessary. This chapter provides a review of the operationally significant effects of human space flight on the human body.

Cardiovascular effects of long-duration space flight

Exposure to microgravity removes the normal hydrostatic pressure gradient associated with upright posture on earth (Figure 35.2). This results in a redistribution of blood volume cranially.

Orthostasis refers to the ability to maintain a stable, upright, standing posture. Orthostatic intolerance refers to the inability to maintain this posture as a result of cardiovascular insufficiency. On returning to Earth many astronauts suffer with orthostatic intolerance with up to 20% of returning crew members unable to complete a 10-minute stand test without experiencing syncope (light headedness) or pre-syncope following short-duration flights [15]. Long-duration flights are associated with an even higher incidence of orthostatic intolerance. This obviously has serious implications when considering the ability of a crew member to evacuate a spacecraft following landing.

The mechanisms underlying this phenomenon have been well investigated. It appears that in flight, fluid shifts occur, resulting from loss of gravitational loading. Human physiology is optimised to function against the hydrostatic pressures associated with life in a gravitationally loaded environment. The sudden removal of gravitational loading associated with space flight finds the body, and the cardiovascular system in particular, maladapted to its new environment. The physiological forces and mechanisms that, under Earth-bound conditions, exist to compensate for hydrostatic forces are now unopposed. Fluid and blood volume therefore shifts to central body compartments and towards the head. This results in facial oedema and volume loss from the lower extremities [18]. Although the intravascular volume shift probably occurs within minutes, the tissue fluid shifts may take a number of hours. The intravascular fluid shift is then misinterpreted by physiological sensors as evidence of excess fluid volume and thus leads to hormonal changes, which encourage fluid shifts that remove fluid from the circulation.

Within the first few hours or days of microgravity exposure, haematocrit elevation and direct measurements indicate that plasma volume decreases([19, 20]). While the resultant loss of circulating volume plays a key role, other cardiovascular elements also appear to contribute significantly to the aetiology of post-flight orthostatic hypotension, for example the lack of gravitational stimulation may reduce baroreflex sensitivity.

Magnetic resonance imaging (MRI) studies have also demonstrated a reduction in left ventricular mass with prolonged bed rest and similar changes may occur with microgravity [21].

Investigations have revealed alterations in the total resistance offered by the peripheral vasculature to blood flow, vascular reactivity and sympathetic drive [22, 23]. Existing solutions to this problem rely on oral rehydration prior to the de-orbit burn and exercise regimens. These have been successful in ameliorating some but not all of the symptoms associated with post-flight orthostatic intolerance [24].

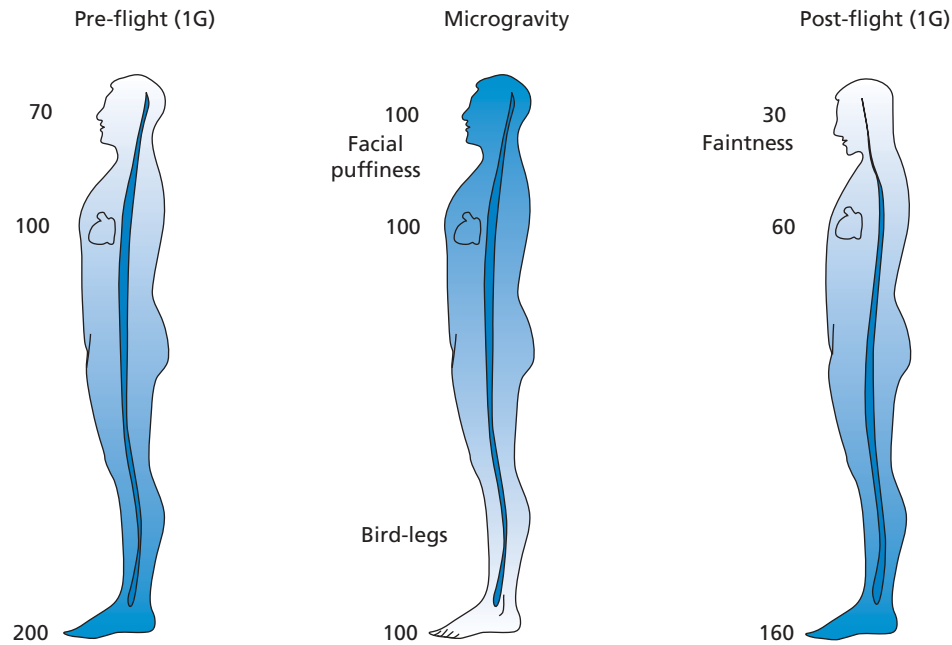

Figure 35.2 Expected distribution of tissue fluid and mean arterial pressure (in mmHg) at the head, heart and feet during pre-flight standing posture, microgravity and post-flight on earth. During microgravity, all gravitational blood pressure gradients disappear and only viscous blood pressure gradients exist between arteries, capillaries and veins. Post-flight orthostatic intolerance probably results from inadequate cerebral perfusion, but vestibular factors may also be involved. (From [17])

Alterations in the function of the cardiovascular system as a result of exposure to microgravity also have significant operational consequences both during and after flight. Prolonged space flight may be associated with abnormal changes in the electrocardiogram (ECG) [15], some of which are associated with enhanced potential for potentially fatal cardiac rhythm irregularities [16].

Effects of prolonged microgravity on the musculoskeletal system

With disuse, the musculoskeletal system atrophies. This is readily observed in everyday life as a consequence of immobilisation following injury or illness. In the microgravity environment the musculoskeletal system is, in effect, permanently mechanically unloaded and as a result both bone and muscle are reduced in quantity and quality. This consequence of space flight on the human body can be considered readily predictable; however, the rate and extent of bone loss is considerable with observed losses of between 1 and 2% per month in flight [6].

The skeleton provides structural support for the soft tissues of the body and plays a protective role. This is not its only function: bone is a dynamic tissue that is constantly modelled and remodelled according to the strain applied in a given environment. It is also serves as a reservoir for more than 95% of the body's calcium store. During the accelerated osteoporosis of space flight this calcium is first deposited in the bloodstream before being excreted by the kidneys. This initially results in high blood levels of calcium (hypercalcaemia) and high urinary levels of calcium (hypercalcuria), which themselves can lead to substantial medical problems. Unabated over the duration of a Martian mission, this bone loss, accompanied by hypercalcaemia and hypercalcuria, would be sufficient to leave crews at significantly increased risk of pathological fracture and renal stone formation.

The osteoporosis associated with space flight has been well documented [7]. These losses appear to be site-specific showing a preponderance for the load bearing regions of the lower limbs and lumbar spine [6]. Two cell types are implicated in the formation and deposition of new bone tissue and the removal of old bone tissue: the osteoblasts and osteoclasts respectively. Study data variously implicate reduced bone formation resulting from osteoblastic dysfunction and excessive osteoclastic resorption [8, 9]. It is likely that both processes are involved, although their relative importance and the mechanism by which they are orchestrated remains unclear.

In the absence of gravitational load, skeletal muscle also experiences wastage. This leads to reductions in muscle

volume, peak force of contraction and shortening velocity. Closer investigation reveals changes in the quality as well as the quantity of muscle. Shifts in muscle fibre type have been observed in studies of muscle biopsy samples. During space flight 'slow twitch' Type I fibres, which are characterised by their low fatigability and suitability for endurance tasks, are seen to alter and exhibit the characteristics of Type II 'fast twitch' fibres, which are more suited to high-intensity, short-duration anaerobic work [10]. These changes appear to occur preferentially in muscle groups associated with load-bearing functions in the terrestrial 1G environment.

The current regimen of counter measures, which relies on resistive exercise and dietary supplementation, appears to provide some protection but is not uniformly effective in preventing musculoskeletal atrophy [6]. The development of specific equipment such as a human-powered centrifuge or lower body negative pressure (LBNP) exercise chamber may well be required to enable a long-duration astronaut to exercise in an environment that has a pressure gradient mimicking gravity to increase lower limb blood supply during impact stress and hence reduce osteoporosis [11]. Such devices also have additional benefits such as maintenance of muscle mass, aerobic capacity [12, 13], sprint speed, gut transit time and balance [14]. However, LBNP does not prevent orthostatic intolerance [13]. In addition oral bisphosphanates have recently been found effective in reducing bone losses in normal subjects deconditioned by 17 weeks of bed rest and will soon be evaluated in spaceflight crews (Paloski 2007, personal communication).

Effects of space flight on the neurovestibular system

The neurovestibular system comprises organs in the inner ear that sense the body's acceleration environment. This information is transduced and transmitted via nerves to the spinal cord and an organisational centre in the brain, which integrates this information. This processed information then forms the basis for motor responses to external perturbations.

There are two systems of accelerometry: the semi-circular canals and the otolith organs, sensing angular acceleration and linear acceleration respectively. There are three semicircular canals orientated orthagonally with respect to one another and two otoliths, the saccule sensing accelerations in the vertical plane and the vestibule which performs the same task in the horizontal plane. During prolonged deployment in microgravity, the pattern to input to this system of accelerometry is fundamentally altered. This appears to lead to sensory conflict and a variety of problems. These include spatial disorientation, space motion sickness and impairment of ability to acquire and track visual targets [25–27].

The early phases of low Earth orbit missions are associated with space motion sickness (SMS) and in a study of 24 shuttle missions SMS was experienced by nearly 70% of astronauts flying for the first time [1]. SMS symptoms appear to subside after a variable period of between 24 to 72 hours. After this time the dominant neurovestibular effects are disorientation and impairment of visual tracking tasks. Upon return to Earth these symptoms resolve but only after a period of several days' re-adapatation, during which performance is markedly impaired.

The absence of gravitational stimulation of the otolith organs appears to be heavily implicated in the observed physiological alterations. This is thought to contribute to sensory conflict and may also interfere with central processing tasks associated with visuomotor skills. Over time it appears that the central nervous system is able to re-weigh inputs to facilitate adaptation, relying more heavily on visual cues than on proprioceptive and otolithic inputs, but this adaptation is not complete as evidenced by the deficits observed [28, 29].

Post-flight decrements in sensory-motor control have now been well characterized from both basic science and occupational health perspectives. Early after flight, postural stability, locomotor coordination, and gaze control are disrupted in all crew members. The underlying mechanisms of this maladaptation are not yet well understood, but this may be critical to the success of extended duration missions beyond low Earth orbit.

Haematological and immunological effects of space flight

The immune activation of lymphoid cells in response to an antigenic or polyclonal challenge is markedly reduced in microgravity and this may reflect the immune dysfunction observed in astronauts [30].

Confinement and psychological aspects of space flight

Psychological assessment is an important component of astronaut selection [31] and more so for prolonged space flight. The confinement of a spacecraft can heighten stressors. In time, these issues may arise for the commercial astronaut. The concept of 'air rage' among commercial airline passengers is familiar and it is not impossible that the austerity of the space environment might contribute to something we might easily refer to as 'space rage' in commercial space participants who have undergone less careful psychological screening. Another psychological aspect is post-flight care. Some astronauts have had difficulty adapting to normal life after missions. It may be that such achievements in commercial astronauts could have similar effects.

Long-term risks from radiation exposure

Radiation induces double-stranded DNA damage [32] and affects other organs, such as the lens of the eye to enhance cataract formation, though this effect is now thought to be less of a concern than previously [33].

Both background radiation and solar particle events cause exposure, though the biological effects of these high charge and energy particles are not well known [34]. However, for short duration, very occasional space tourists, these radiation issues are unlikely to be significant.

Sexual health in space

Discussions regarding sexual health during prolonged space missions have already begun [35].

Space flight with pre-existing medical conditions

Currently, astronauts are highly selected hence the effects of microgravity on pre-existing illnesses can only be speculated on by studying the effects of acceleration and head down tilt.

Table 35.3 gives some examples of conditions that may be incompatible with space tourism.

Table 35.3 Examples of conditions that may be incompatible with space tourism

Cardiovascular
– Conditions affecting ability to increase cardiac output (aortic stenosis, Beta blockade)
– Ischaemic heart disease
Respiratory
– Severe forms of any respiratory problem (asthma, chronic obstructive pulmonary disease)
Neurological
– Epilepsy
– Idiopathic intracranial hypertension (microgravity may exacerbate)
Rheumatological
– Osteoperosis
Systemic
– Conditions affecting oxygen delivery (e.g. anaemia, sickle cell anaemia)
Infective
– Any condition putting other crew members at risk
Psychological
– Unstable neuropsychological conditions

Illness and injury in space

The lack of access to equipment and appropriate specialists/investigative technologies obviously would hamper any illness in space. In addition, there are innate effects of the microgravity environment that cause further compromise.

Trauma

Wounds take longer to heal and fractures more so. The development of a broadly trained space doctor has recently been discussed [36]

Infection

A compromised immune system may again slow recovery. Issues of infection control in an enclosed environment also need to be addressed.

Microgravity: discussion

It is clear that microgravity exerts a profound and widespread impact on human physiology. Some of these changes represent appropriate physiological adaptations and can be thought of as an attempt to achieve new 'space normal' homeostatic set points. However, this 'space normal' state is clearly not appropriate for 1G environments and is likely not appropriate for the reduced gravity environment on Mars, which is roughly a third that of Earth's.

It is said that the two most difficult feats in all of rocket science are starting and stopping. Having survived the violence of take-off the hazards of long-duration deployment in the space environment lie in wait.

Attempts to protect crews using exercise counter measures and pharmacological approaches have been met with limited success. Alternate strategies are required and may stem from modifications in mission design or novel mission architectures rather than from basic life science research.

Conclusion

If the era of space tourism is genuinely upon us then it presents substantial challenges to physicians who provide advice to future space travellers. The high accelerative forces, uniquely hostile space environment, relative isolation from terrestrial healthcare systems and effects of microgravity on human physiology together conspire to make this an austere environment in which to maintain health or deliver healthcare.

Several private individuals have already flown in space with commercial companies. In these few flights the formal paradigm of space medicine for professional astronauts has already been challenged and its boundaries successfully extended (Note: Greg Olson paper here).

Questions remain over how such a practice should be regulated and who is best placed to assess and qualify individuals for flight.

These activities are viewed with cynicism in some quarters. Perhaps because there is a perception that it detracts from the programme of exploration hitherto prosecuted by elite teams of professionals. And yet one could successfully argue that, in extending the range of individuals who might gain access to space and accommodating them and their concurrent medical conditions, one is engaging in a new programme of exploration, equal in measure in terms of its excitement and challenge.

References

1. Davis JR *et al.* (1988) Space motion sickness during 24 flights of the space shuttle. *Aviat Space Environ Med* **59**(12): 1185–1189.
2. Steinbach GC *et al.* (2005) Intracranial pressure dynamics assessed by noninvasive ultrasound during 30 days of bed rest. *Aviat Space Environ Med* **76**(2): 85–90.
3. Vein AA *et al.* (2009) Space headache: a new secondary headache. *Cephalalgia* **29**(6): 683–686.
4. Macho L *et al.* (2001) Effects of exposure to space flight on endocrine regulations in experimental animals. *Endocrine Reg* **35**(2): 101–114.
5. Sonnenfeld G and Shearer WT (2002) Immune function during space flight. *Nutrition (Burbank, Los Angeles County, CA)* **18**(10): 899–903.
6. Vico L *et al.* (2000) Effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts. *Lancet* **355**(9215): 1607–1611.
7. Turner RT (2000) Invited review: what do we know about the effects of spaceflight on bone? *J Appl Physiol* **89**(2): 840–847.
8. Carmeliet G *et al.* (1997) Microgravity reduces the differentiation of human osteoblastic MG-63 cells. *J Bone Mineral Res* **12**(5): 786–794.
9. Carmeliet G *et al.* (2001) Space flight: a challenge for normal bone homeostasis. *Crit Rev Eukar Gene* **11**(1–3): 131–144.
10. Fitts RH *et al.* (2001) Functional and structural adaptations of skeletal muscle to microgravity. *J Exp Biol* **204**(Pt 18): 3201–3208.
11. Smith SM *et al.* (2008) WISE-2005: supine treadmill exercise within lower body negative pressure and flywheel resistive exercise as a countermeasure to bed rest-induced bone loss in women during 60-day simulated microgravity. *Bone* **42**(3): 572–581.
12. Lee SMC *et al.* (2009) LBNP exercise protects aerobic capacity and sprint speed of female twins during 30 days of bed rest. *J Appl Physiol* **106**(3): 919–928.
13. Schneider SM *et al.* (2002) Lower-body negative-pressure exercise and bed-rest-mediated orthostatic intolerance. *Med Sci Sports Exercise* **34**(9): 1446–1453.
14. Macias BR *et al.* (2005) Space exercise and Earth benefits. *Curr Pharm Biotechnol* **6**(4): 305–317.
15. D'Aunno DS *et al.* (2003) Effect of short- and long-duration spaceflight on QTc intervals in healthy astronauts. *Am J Cardiol* **91**(4): 494–497.
16. Fritsch-Yelle JM *et al.* (1998) An episode of ventricular tachycardia during long-duration spaceflight. *Am J Cardiol* **81**(11): 1391–1392.
17. Hargens AR and Watenpaugh DE (1996) Cardiovascular adaptation to spaceflight. *Med Sci Sports Exercise* **28**(8): 977–982.
18. Thornton WE and Hoffler GW (1977) Haemodynamic studies of the legs under weightlessness. In: Johnston RS and Dietlein LF (eds) *Biomedical Results from Skylab*, pp. 324–329. NASA, Washington.
19. Kirsch K *et al.* (1986) Venous pressure in microgravity. *Die Naturwissenschaften* **73**(7): 447–449.
20. Kirsch KA *et al.* (1984) Venous pressure in man during weightlessness. *Science* **225**(4658): 218–219.
21. Dorfman TA *et al.* (2007) Cardiac atrophy in women following bed rest. *J Appl Physiol* **103**(1): 8–16.
22. Waters WW *et al.* (2002) Postspaceflight orthostatic hypotension occurs mostly in women and is predicted by low vascular resistance. *J Appl Physiol* **92**(2): 586–594.
23. Zhang LF (2001) Vascular adaptation to microgravity: what have we learned? *J Appl Physiol* **91**(6): 2415–2430.
24. Shi S-J *et al.* (2004) Fludrocortisone does not prevent orthostatic hypotension in astronauts after spaceflight. *Aviat Space Environ Med* **75**(3): 235–239.
25. Harm DL and Parker DE (1994) Preflight adaptation training for spatial orientation and space motion sickness. *J Clin Pharmacol* **34**(6): 618–627.
26. Lackner JR (1992) Spatial orientation in weightless environments. *Perception* **21**(6): 803–812.
27. Reschke MF *et al.* (2002) Smooth pursuit deficits in space flights of variable length. *J Gravitational Physiol* **9**(1): P133–P136.
28. Holstein GR *et al.* (1999) Anatomical observations of the rat cerebellar nodulus after 24 hr of spaceflight. *J Gravitational Physiol* **6**(1): P47–P50.
29. Parker DE *et al.* (1985) Otolith tilt-translation reinterpretation following prolonged weightlessness: implications for preflight training. *Aviat Space Environ Med* **56**(6): 601–606.
30. Fitzgerald W *et al.* (2009) Immune suppression of human lymphoid tissues and cells in rotating suspension culture and onboard the International Space Station. *In Vitro Cell Dev- An* **45**(10): 622–632.
31. Endler NS (2004) The joint effects of person and situation factors on stress in spaceflight. *Aviat Space Environ Med* **75**(7 Suppl.): C22–C27.
32. Dieriks B *et al.* (2009) High content analysis of human fibroblast cell cultures after exposure to space radiation. *Radiat Res* **172**(4): 423–436.

33. Chylack LT *et al*. (2009) NASA study of cataract in astronauts (NASCA). Report 1: cross-sectional study of the relationship of exposure to space radiation and risk of lens opacity. *Radiat Res* **172**(1): 10–20.
34. Cucinotta FA and Durante M (2006) Cancer risk from exposure to galactic cosmic rays: implications for space exploration by human beings. *Lancet Oncol* **7**(5): 431–435.
35. Shimizu T *et al*. (2004) A proposal on a contribution of space biological sciences to sexual health in the human space life. *Uchū Seibutsu Kagaku* **18**(3): 169–170.
36. Kirkpatrick AW *et al*. (2009) Severe traumatic injury during long duration spaceflight: light years beyond ATLS. *J Trauma Manage Outcomes* **3**: 4.

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