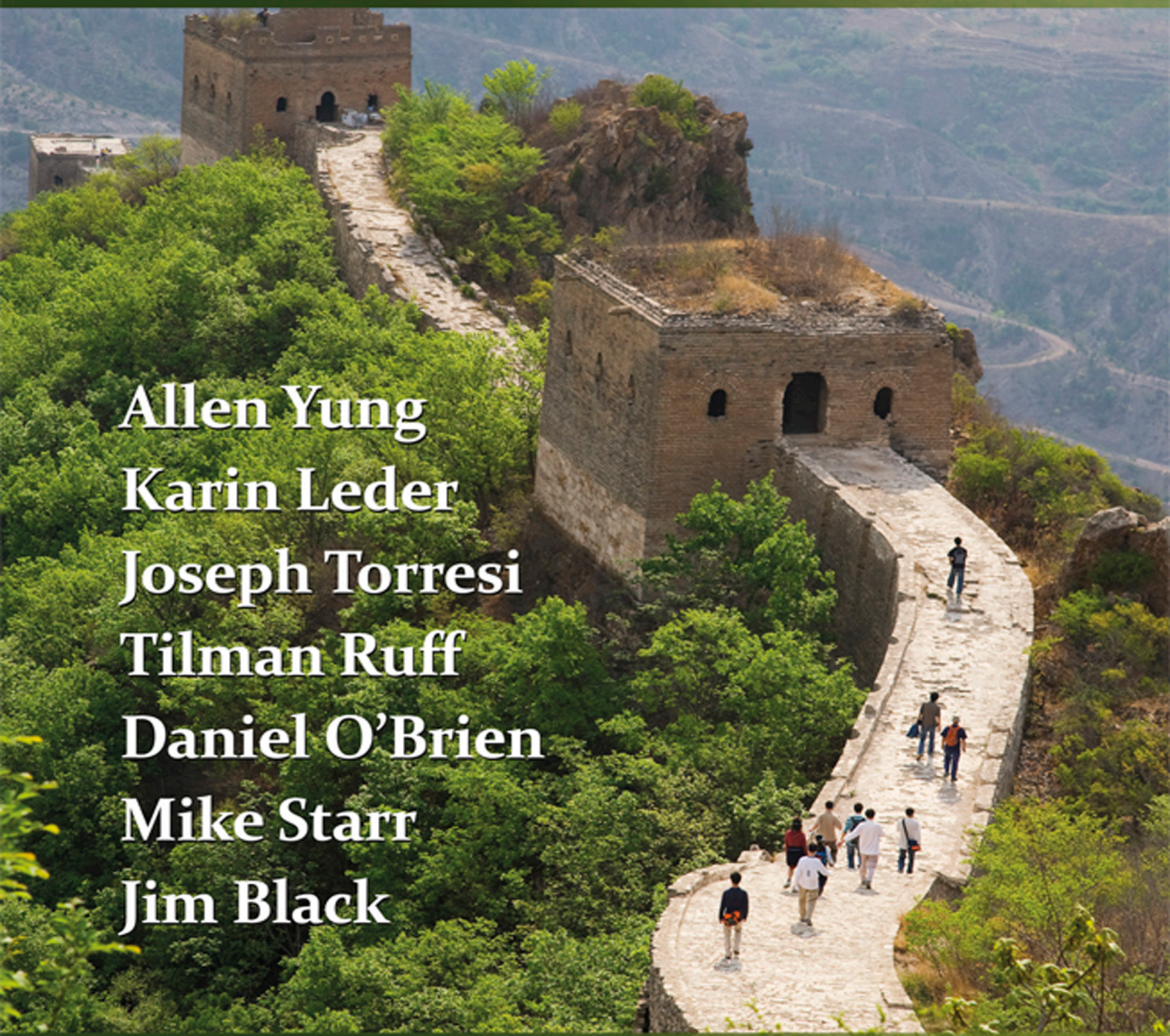
Manual of Travel Medicine

THIRD EDITION



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IP Communications

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Dedication

Allen Yung has been the principal driver of all three editions of this *Manual* and the several versions of the guidelines for Fairfield Infectious Diseases Hospital registrars which preceded it. For all the authors of this *Manual* – and for many others besides – Allen has been a friend and mentor of the kind that everyone should have. Within a year of publication of this edition of the *Manual* in printed form, Allen died. His co-authors dedicate this edition to Allen, with deep gratitude.

Allen left China as a child, and came eventually to Tasmania, benefitting from the Friends' School in Hobart, which has contributed to the life journeys of many remarkable people. For several decades at Fairfield, until it closed in 1996, and then at the Royal Melbourne Hospital, Allen taught succeeding generations of infectious disease physicians. He was the consummate clinician, astute, patient, focussed, a pre-eminent listener, bringing extensive experience to bear, but always willing to be surprised and to learn. His golden rules abide the test of time. He is fondly remembered around Australia and beyond.

We salute a great physician and teacher, and a fine, compassionate, gentle, and humble man.

Karin Leder, Joseph Torresi, Tilman Ruff, Daniel O'Brien, Mike Starr, Jim Black

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Contents

Vaccine terminology and abbreviations

Different vaccine components that are formulated together in the same presentation (vial or prefilled syringe) are listed separated by a '-'. Vaccines that are mixed by the immunisation provider before administration are listed separated by a '/'. Thus, the combined co-formulated hepatitis A and B vaccine is designated HA-HB, and the combined HA and typhoid vaccine, which is mixed by the provider, is designated HA/Vi. The paediatric vaccine DTPa-HB-IPV used to reconstitute lyophilised Hib vaccine is designated DTPa-HB-IPV/Hib.

Vaccines of higher antigen content are designated by capitals; those containing the same antigens in substantially lower amounts are referred to using lower case. For example paediatric diphtheria-tetanus-acellular pertussis vaccine is designated DTPa, while the corresponding lower antigen vaccine for adolescent and adult use is designated dTpa.

Antibody to a particular antigen '…' is designated as 'anti…'. For example, antibody to hepatitis B surface antigen is designated antiHBs, and antibody to hepatitis A is designated antiHA.

ABL	Australian bat lyssavirus
ADT	Adsorbed diphtheria–tetanus vaccine
AIH	Australian Immunisation Handbook
AMS	Acute mountain sickness
antiHBc	Hepatitis B core antibody
antiHBs	Hepatitis B surface antibody
ART	Antiretroviral therapy
AS	Altitude sickness
AUC	Area under the curve
BCG	Bacille Calmette-Guérin
bid	Twice daily
CDC	Centers for Disease Control and Prevention (US unless otherwise specified)

CCV	Cell culture vaccine
CHF	Congestive heart failure
CLM	Cutaneous larva migrans
CMV	Cytomegalovirus
cVDPV	Circulating vaccine-derived polioviruses
D	Diphtheria
DEET	N,N-diethylmetatoluamide
DHF	Dengue haemorrhagic fever
DSS	Dengue shock syndrome
dT	Diphtheria–tetanus vaccine (adult formulation)
DT	Diphtheria–tetanus vaccine (paediatric)
dTpa	Diphtheria–tetanus–acellular pertussis vaccine (lower dose adolescent/adult formulation)
DTPa	Diphtheria-tetanus-acellular pertussis vaccine (higher dose paediatric formulation)
DVT	Deep vein thrombosis
EBV	Epstein-Barr virus
ELISA/EIA	Enzyme-linked immunosorbent assay
EIA U	ELISA units
ERIG	Equine rabies immunoglobulin
ETEC	Enterotoxigenic *Escherichia coli*
FHA	Filamentous haemagglutinin
GBS	Guillain-Barré syndrome
GMT	Geometric mean titre (the antilog of the mean of the logs of a set of antibody titres)
HA	Hepatitis A
HACE	High-altitude cerebral oedema
HAPE	High-altitude pulmonary oedema
HB	Hepatitis B
HbOC	Hib PRP conjugated to non-toxic diphtheria mutant protein CRM_{197}
HBsAg	Hepatitis B surface antigen
HDCV	Human diploid cell (rabies) vaccine
Hib	*Haemophilus influenzae* type b
HIV	Human immunodeficiency virus
HPV	Human papilloma virus

HZ	Herpes zoster
ID	Intradermal
IG	Immunoglobulin (normal unless otherwise specified)
IM	Intramuscular
INR	International normalised ratio
IPD	Invasive pneumococcal disease
IPV	Inactivated polio vaccine
IU	International units
JE	Japanese encephalitis
LT-ETEC	Heat-labile toxin-producing enterotoxigenic *Escherichia coli*
MenACWY	4-valent ACYW135 meningococcal conjugate vaccine
MenCCV	Meningococcal C conjugate vaccine
4vMenPV	4-valent (ACYW135) meningococcal polysaccharide vaccine
µg	Microgram
mg	Milligram
MMR	Measles–mumps–rubella vaccine
MMRV	Measles–mumps–rubella–varicella vaccine
NHMRC	(Australian) National Health and Medical Research Council
NHIG	Normal human immunoglobulin
NIP	National Immunisation Program
OMP	Outer membrane protein
OPV	Oral polio vaccine
ORS	Oral rehydration solution
Pa	Acellular pertussis vaccine
PCECV	Purified chick embryo cell (rabies) vaccine
PCV	Pneumococcal conjugate vaccine
PDEV	Purified duck embryo cell (rabies) vaccine
PE	Pulmonary embolism
PEP	Post-exposure prophylaxis
Pf	*Plasmodium falciparum*
Pv	*Plasmodium vivax*
PI	Product information

PPD	Purified protein derivative (of *Mycobacterium tuberculosis*)
PPV	Pneumococcal polysaccharide vaccine (23-valent)
PRN	Pertactin
PRP	Polyribosylribitol phosphate (outer polysaccharide and major virulence factor of Hib)
PRP-OMP	Hib vaccine in which PRP is conjugated to meningococcal group B OMP
PRP-T	Hib vaccine in which PRP is conjugated to tetanus toxoid
PS	Polysaccharide
PT	Pertussis toxin
PVRV	Purified Vero cell rabies vaccine
qid	Four times a day
rCTB	Recombinant cholera toxin B subunit
RIG	Rabies immunoglobulin
RR	Relative risk
SARS	Severe acute respiratory syndrome
SBET	Standby emergency selt-treatment
SC	Subcutaneous
STI	Sexually transmitted infection
T	Tetanus
TB	Tuberculosis
TBE	Tick-borne encephalitis
TD	Travellers' diarrhoea
TGA	Therapeutic Goods Administration, Australian regulatory authority for medicines and medical devices
TST	Tuberculin skin test
Ty	Typhoid
VAPP	Vaccine-associated paralytic poliomyelitis
VDPV	Vaccine-derived poliovirus
VFR	Visiting friends and relatives
VHF	Viral haemorrhagic fever
Vi	Vi capsular polysaccharide of *Salmonella* Typhi
VTE	Venous thromboembolism
VZ	Varicella-zoster
VV	Varicella vaccine

WC/rBS	Whole cell/B subunit
WHO	World Health Organization
WTO	World Travel Organization
YF	Yellow fever
YEL-AND	Yellow fever vaccine-associated neurotropic disease
YEL-AVD	Yellow fever vaccine-associated viscerotropic disease

Preface

The first edition of the *Manual of Travel Medicine* was published in 1999 through the Victorian Infectious Diseases Service at the Royal Melbourne Hospital, when the discipline of travel medicine was only in its infancy. At that time, there were few high-quality travel medicine information and education resources available. The *Manual of Travel Medicine* was a response to a perceived need for an authoritative and up-to-date resource to support good travel medicine practice. An expanded second edition was published in 2004. Now, in 2011, a variety of excellent travel health resources – both web-based and text – are available. It is therefore reasonable to question why we believed it worthwhile to proceed with a third edition of the *Manual*.

Travel medicine has changed significantly since 2004. First, international tourist numbers continue to rise, such that now there are approximately 900 million international trips taken annually worldwide, and almost 7 million outbound trips taken by Australians each year. A rising volume of travel is also being undertaken by high-risk groups, such as those with immunosuppression, the elderly, pregnant women and young children, which increases complexities surrounding health issues and disease risks. Second, travel medicine as a discipline has evolved substantially, with increasing recognition of the need to make recommendations based on the best available evidence. Accordingly, there has been intensified surveillance of health problems among travellers as well as expansion of research in the field. Previous recommendations were often based on case reports, case series, or studies done by single institutions. Currently, more global and generalisable data is being analysed as a basis for updating travel advice. For example, a worldwide communication and data collection network known as GeoSentinel performs surveillance of travel related morbidity. This network involves approximately 50 sites around the world that monitor all travel-related illnesses seen in their clinics and the data, which is aggregated centrally, is available as the basis for new research into risk factors for travel-related diseases.

The explosion of travel health information is making it increasingly difficult to keep abreast of the latest advances in the field. The growing number of resources tends to complicate rather than simplify travel guidance, especially since there is lack of consensus between different resources on many aspects of travel health advice. For example, the European perspective on antimalarials provided in the WHO blue book is markedly different from the US perspective given in the

CDC yellow book, despite the fact that both are considered 'authoritative' resources. There is also no national website providing detailed Australian consensus travel guidelines.

For this third edition of the *Manual of Travel Medicine* we retain the best features of its predecessors, with its focus being a user-friendly, practical handbook and desk-top reference for travel health practitioners in Australasia. It is a handy reference tool and not a comprehensive textbook. Recognising the controversies and different approaches advocated by different authorities, we endeavour to explain what *we* think and do. It therefore makes reference to advice given in other resources, as well as providing practical recommendations on how to decide between various pre-travel advice options. It is aimed at all Australasian healthcare workers interested in and involved in the care of travellers, including doctors, nurses and pharmacists.

The *Manual*'s prime objectives are to provide:

- a clear reference for recommendations regarding immunisations, malaria prophylaxis, and other key travel health areas
- a practical approach to management of most issues that arise in the medical care of travellers.

Two additional authors have been recruited for this third edition. Jim Black is a senior epidemiologist and expert in infectious disease surveillance; Mike Starr is a paediatrician and infectious diseases physician with special interests in maternal and paediatric travel health issues, as well as emergency medicine and medical education.

All the information within the *Manual of Travel Medicine* has been extensively revised and updated, with additional changes including:

- One new chapter, Health issues in returned travellers, focusing on the more common and important illnesses and their presentations. The place of screening of asymptomatic travellers is included.
- Two new vaccines, for pneumococcal infections and rotavirus infection. Plague vaccine has been deleted as it is no longer available.

How to use the *Manual*

The *Manual of Travel Medicine* is designed to provide essential information about pre-travel medicine. Its organisation reflects what is needed during a consultation, progressing from principles to:

- immunisation
- prevention and management of malaria
- prevention and management of travellers' diarrhoea

- specific infectious and non-infectious conditions that may require attention and discussion
- specific groups of travellers
- health issues in returned travellers
- additional resources.

As in the previous editions, we summarise:

- our recommendations for common travel destinations
- immunisation and malaria recommendations by country.

We also include up-to-date maps for a wide range of infections. We have made every effort to ensure that the information contained in the *Manual of Travel Medicine* is accurate and current at the time of writing. Principles of travel medicine practice change relatively slowly. However, readers must be aware that in travel medicine – as in every field of medicine, but in this area more than in most – disease patterns, country requirements, available vaccines and drugs, and specific recommendations for their use frequently change over time. Thus practitioners should supplement the *Manual* with any more up-to-date authoritative information.

Comments from readers are welcome (Victorian Infectious Diseases Service, Royal Melbourne Hospital, Victoria, 3050, Australia or via email to, karin.leder@monash.edu) and will help us to improve future editions.

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Karin Leder
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Tilman A Ruff
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Mike Starr
Jim Black
Melbourne, October 2011

About the Authors

Allen Yung is a Consultant Emeritus at the Royal Melbourne Hospital. He worked at Fairfield Hospital, Melbourne, for 32 years until its closure in 1996, and was Chief of Medicine for the final four years. From 1996 to November 2003 he worked as a part-time consultant in infectious diseases in the Victorian Infectious Diseases Service at the Royal Melbourne Hospital. He has a lifelong interest in tropical and travel medicine, tuberculosis, and fevers of any sort. He is an honorary life member of the Australasian Society for Infectious Diseases, and was awarded the Medal of the Order of Australia (OAM) in 1998. In 1999 he and Tilman Ruff co-authored the first edition of this *Manual*.

Karin Leder currently holds positions as Head of Travel Medicine and Immigrant Health for the Victorian Infectious Disease Service, Royal Melbourne Hospital, and Head of the Infectious Disease Epidemiology Unit in the Department of Epidemiology and Preventive Medicine, Monash University. In addition, she heads Fairfield Travel Health at RMH and is a Melbourne site co-director for the GeoSentinel surveillance network. GeoSentinel is an international network established in 1996 through the International Society of Travel Medicine and the CDC in Atlanta, United States, with the role of monitoring the global spread of infectious diseases.

Karin trained in internal medicine and infectious diseases in Melbourne, and also undertook a combined clinical and research Fellowship at the Beth Israel Deaconess Medical Center in Boston. She has a Masters of Public Health from Harvard University and a PhD in travel medicine from Monash University. Karin has studied tropical diseases in Peru, and has received a Diploma in Tropical Medicine and Hygiene. She has performed several research studies in the field of travel medicine, and has a particular interest in 'VFR' travellers. She has also written several journal articles addressing methodological issues associated with performing travel-related research.

Joseph Torresi is currently Head of Travel Medicine and an infectious diseases physician at Austin Health, and an Associate Professor in the Department of Medicine, Austin Health, University of Melbourne. He is a Melbourne site co-director for the GeoSentinel surveillance network. Joseph has coordinated several research studies through GeoSentinel, including projects investigating respiratory tract infections, vivax and other forms of malaria, and gastrointestinal infections in travellers, dengue fever in Australian travellers to South-East

Asia, tuberculosis in immigrants, and travellers' diarrhoea. He has been a principal investigator on several clinical vaccine and therapeutic trials and is a member of the *v2V* Dengue Steering Committee.

Joseph also heads the Hepatitis Molecular Virology Laboratory at Austin Health. He has active research programs in hepatitis C vaccine development, the pathogenesis of hepatitis B and C infection, influenza epidemiology and immunology, and has published numerous papers in hepatitis virology. He is currently funded through the National Health and Medical Research Council, Australian Centre for Hepatitis and HIV Virology, Commonwealth Department of Health and Ageing, and the Department of Innovation, Industry, Science and Research.

Tilman Ruff works in preventive medicine in immunisation policy and programs, and the urgent public-health imperative to abolish nuclear weapons. He is Associate Professor in the Nossal Institute for Global Health, University of Melbourne, has served as international medical advisor to Australian Red Cross since 1996, was founding Director of Travel Medicine at Fairfield Hospital, and then Head of Travel Medicine in the Victorian Infectious Diseases Service at Royal Melbourne Hospital till 1998.

Tilman worked on hepatitis B control, immunisation, and maternal and child health in Indonesia between 1988–98, including on the first population-level introduction and evaluation of hepatitis B immunisation there. He has provided technical support on immunisation in Pacific island countries since 1995 through AusAID, UNICEF and WHO. From 1998 until 2003 he was inaugural regional medical director for GlaxoSmithKline Biologicals, and continues to consult for various vaccine manufacturers. Tilman has undertaken research on a variety of vaccines and vaccine-related diseases, ciguatera fish poisoning, the health and environmental effects of nuclear test explosions, the use of highly-enriched uranium in the production of radioisotopes for medicine, and the health effects of nuclear weapons and radioactive fallout.

Tilman chairs the International Campaign to Abolish Nuclear Weapons, is International Councillor for the Medical Association for Prevention of War (Australia), and is Southeast Asia-Pacific vice-president of International Physicians for the Prevention of Nuclear War (Nobel Peace Prize 1985). In 2009–10 he was NGO Advisor to the Co-chairs of the International Commission on Nuclear Non-proliferation and Disarmament. He is a member of the WHO Western Pacific Region Expert Resource Panel on Hepatitis B.

Daniel O'Brien is an infectious diseases physician working in the Victorian Infectious Diseases Service at Royal Melbourne Hospital and in the Geelong Infectious Diseases Service at Geelong Hospital. Daniel is also a clinical Associate Professor in the Department of Medicine, University of Melbourne. His special interests include travel medicine, immigrant and refugee health, and

mycobacterial diseases, and he is a member of the WHO drug treatment working group for Buruli ulcer. He is an active member of the Nobel Peace Prize–winning medical humanitarian organisation Médecins Sans Frontières, primarily supporting HIV and TB programs, and has worked in up to 30 countries in Africa, Asia, Eastern Europe, the Caribbean and Latin America.

Mike Starr is a Paediatrician, Infectious Diseases Physician and Consultant in Emergency Medicine at the Royal Children's Hospital (RCH) in Melbourne. Mike is head of the RCH Travel Clinic. He is also the Director of Paediatric Education. He trained in Melbourne and Vancouver, and has worked and taught in Darwin and the Top End, as well as in Chile, Vietnam, Cambodia and India. His special interests include tropical and travel medicine, particularly in children and pregnant women.

Jim Black is Associate Professor in the Nossal Institute for Global Health at the University of Melbourne. He holds a medical degree and a PhD in epidemiology from Monash University, and the Diploma in Tropical Medicine and Hygiene and Master of Community Health degrees from the Liverpool School of Tropical Medicine. His research interests include the epidemiology and control of tuberculosis in Africa, surveillance of infectious diseases, and the acquisition of infectious diseases by travellers, as well as the uses of mobile phones to improve health care in developing countries.

Chapter 1

Principles of Pre-travel Health Care

Chapter outline

Each year Australians undertake approximately 5 million overseas departures. There are few published data on the proportion of travellers seeking pre-travel advice, although it is known that many at-risk travellers fail to make a pre-travel visit to a doctor. A survey of Australian travellers by the Travel Health Advisory Group in 2002 showed that, of 500 travellers, 69% did not seek professional advice, 27% saw a general practitioner, and 4% attended a travel-medicine clinic (Zwar 2003). A cross-sectional survey was conducted among 2101 travellers at the departure lounges of five airports (Singapore, Kuala Lumpur, Taipeh, Melbourne, Seoul). All were en route to a destination in Asia, Africa or South America, yet only 31% had sought pre-travel health advice (Wilder-Smith 2004).

In view of the potential health hazards facing travellers, it is clear that more public education is needed about the importance of obtaining health advice before travelling. However, it is difficult to assess the impact of pre-travel advice accurately, as self-selection for advice is likely on the basis of higher individual risk from pre-existing illness or from travel to a high-risk destination. Even when correct health advice is given, recall of the advice by travellers is variable, and adherence with recommendations is not assured.

An important part of pre-travel advice is a health risk assessment of the trip. The assessment balances the health of the traveller (age, underlying health conditions, medications, and immunisation history) with details of the planned trip (season of travel, itinerary, duration, and planned activities). Provision of comprehensive pre-travel health care involves advising on measures to prevent infectious diseases during travel, as well as giving advice regarding measures for the personal safety of travellers and the avoidance of environmental risks. Therefore, pre-travel visits should include a discussion of vaccine-preventable illness, avoidance of insects and animal bites, malaria chemoprophylaxis (where relevant), prevention and self-treatment of travellers' diarrhoea, and advice on risk reduction in personal behaviour, including safe-sex practices.

Each traveller must be considered individually, but there are several common themes and principles that underpin sound, consistent and high-quality health advice for travel. Those advising travellers should be familiar with these principles, have a good working knowledge of travel medicine issues, and know when and how to access up-to-date information.

Our principles for pre-travel care are as stated in the chapter outline above.

1.1 Understand the epidemiology of travel and travel-related conditions

The most common destinations of Australian travellers are New Zealand, the United States, Europe (especially the United Kingdom), Asia (Thailand, Indonesia, China, Japan, Vietnam and Singapore), and Fiji. The Middle East and Africa are visited proportionately less commonly by Australians, although travel to Africa has been increasing over recent years. Infections may also follow travel within Australia.

Travellers are exposed to many infectious and non-infectious health risks. In a study by Steffen et al. (1987) among Swiss-German travellers, 1–5% of international travellers sought medical attention, 0.01–0.1% required emergency medical evacuation, and 1 in 100 000 died.

Cardiovascular disease and trauma are the most frequent causes of death, and are more common than infectious diseases. However, many of the infection-related deaths can be prevented.

Risks and types of infection vary greatly depending on the exact geographical locations visited, the circumstances of travel, and the time of the year during which exposure occurs. Likely exposures will differ among travellers, long-term visitors and local residents. The type of accommodation and the recreational or occupational activities performed also influence the likely diseases

encountered. Acquisition of some infections requires exposure to insect bites, animals, contaminated soil, infected water, or sexual encounters. Some pertinent features and risk factors of the exposure history are dealt with further in Chapter 6.

A significant proportion of all travellers develop at least one travel-related illness, and a number of these are serious. Many are potentially preventable. Travellers' diarrhoea is the most common, affecting 30–80% of travellers, and malaria is the most serious common infection. Multiple illnesses may coexist in the one patient. Symptoms may occur during travel or after return. The risk of individual infections appears under the various vaccines and in Chapter 8. As discussed further in Chapter 8, the incubation period of various diseases, their geographical distribution and their modes of transmission may be more important clues to a diagnosis than clinical features alone. A detailed knowledge of disease epidemiology is therefore required to individualise pre-travel health advice and to provide appropriate care for returned travellers.

1.2 Provide up-to-date information and advice

An increasing number of information sources of pre-travel advice are available. Disease patterns, epidemics, antimicrobial drug resistance, prophylactic recommendations, and drug or vaccine availability can change, so it is advisable to check reputable online information sources.

Useful sources of travel-related information are discussed in Chapter 9.

1.3 Start early

Travel health advice can never be sought too early. Last minute pre-travel consultations may impose significant constraints on ideal practice. Vaccines may require multiple doses over a period of six months or more, the administration of some drugs and vaccines should be spaced, and immunity tends to take a few weeks after the last dose of vaccine to become optimal. Trial of some medications, such as mefloquine prophylaxis, is optimally begun a few weeks before travel to allow steady-state levels to be achieved and to avoid the development of potential side-effects just prior to or after departure. Sometimes travellers change their itinerary or destination(s) or decide not to travel on the basis of medical advice. Disruption can be minimised by travellers seeking this advice and making informed choices early.

Travellers should be encouraged to present at least four to six weeks before departure. Those with significant chronic illness or undertaking high-risk activities and prolonged stays should seek advice as early as possible.

1.4 Allow sufficient time for the consultation

A pre-travel consultation for a person who is well known to the doctor and is embarking on a simple trip may only take a few minutes. However, most take at least 15 minutes. In our referral clinic, we allow 30 minutes for individuals and couples, and one hour for families or groups of more than two. Additional time is spent with the pharmacist and the nurse. Sometimes multiple visits are required.

For those travelling with young children, especially for prolonged periods, it may be ideal to involve only the parents in the initial consultation. A detailed immunisation plan for the child(ren) can be formulated then, and a separate visit with the children can follow. This enables parents to concentrate, avoids long waits with impatient, exasperated, tired or hungry children, and minimises build-up of anxiety before immunisations. However, we understand that this may not always be practicable.

1.5 Individualise advice

Advice needs to be tailored to the traveller, the trip and the time. A pregnant woman, a healthy adolescent and an HIV-infected person going to the same destination will need different advice. Some disease risks are focal; for example, someone visiting Bangkok or Thai coastal resorts, or Kathmandu and the Nepalese Himalayas, is at no risk of malaria, whereas a traveller staying overnight in hill tribe areas of northern Thailand, or visiting lowland Nepal, is at risk.

Most travel clinics use a standard history questionnaire to obtain information necessary for risk assessment and management. It generally includes the following items.

- Traveller's characteristics
  - age
  - pregnancy
  - medical history, including conditions that may influence susceptibility to or severity of infections (e.g. splenectomy, gastrectomy) and history of mental illness, central nervous system disease, or cardiac problems (important considerations in malaria prophylaxis)
  - current health issues and medications, including potential need for emergency treatment (e.g. due to asthma, diabetes or epilepsy) or prophylaxis (e.g. thromboembolism, altitude sickness)
  - past history of jaundice/hepatitis, STIs, and travel-related illnesses such as malaria, dengue, travellers' diarrhoea
  - drug allergies and prior experience of antimalarial drugs

  - full immunisation history
- Travel details
  - detailed itinerary, not only of countries but regional details
  - duration of stay
  - reason for travel
  - planned activities, especially activities that may result in injury or pose additional risks if undertaken in remote areas
  - likelihood of itinerary changing and likely alternatives
  - type of accommodation
  - season.

1.6 Identify high-risk travellers

Particular care should be taken to identify travellers whose planned trip puts them at increased risk. They include:

- travellers with chronic illnesses
- travellers who are immunocompromised
- young children or the elderly
- pregnant travellers
- expatriates and travellers on extended trips to developing countries, particularly if remote from good medical care
- backpackers
- VFR travellers (travellers visiting friends and relatives, see chapter 7.5).

Asthma and mental health problems are the most frequent conditions requiring repatriation on medical grounds among long-term Australian overseas development workers.

While most travellers' needs can be met by a knowledgeable GP, high-risk travellers require a good deal of time and should generally be referred to, or at least discussed with, an infectious diseases physician or a doctor experienced in travel medicine. Details regarding the management of these travellers are addressed in Chapter 7. Some general recommendations are set out below.

Travellers with chronic conditions

To help their patients with chronic conditions to be well prepared for their journey, doctors should:

1. conduct a thorough pre-departure review to ensure the condition is optimally controlled, the patient has a good understanding of his/her condition and its monitoring, particularly what to do if the condition becomes

unstable, and that a clear emergency plan has been developed and documented and is understood by the patient

2. provide a detailed letter on doctor's letterhead with contact details in case further information is required; the letter should outline the history of the condition and any complications, its current status and treatment, and, if appropriate, copies of recent test results (e.g. ECG for cardiac patients)
3. ensure the patient has ample quantities of medications and any needed equipment (e.g. blood glucose monitoring equipment, peak expiratory flow meter); copies of prescriptions may help allay concern about possible customs difficulties (which we have rarely encountered for legitimate medical items)
4. provide name and contact details of an overseas colleague who can arrange continuing care (if appropriate)
5. encourage patients to become familiar with local medical resources at their destination (especially for long-term travellers or expatriates) and ensure that at least one other person is aware of their condition, what to do, and who to call in the event of an emergency
6. encourage patients to take out appropriate health insurance, including cover for emergency medical assistance.

Patients who are under specialist care should generally consult both their general practitioner and their specialist/s before travelling. If their condition is severe or unstable, they should discuss proposed travel with their doctors before making any bookings.

1.7 Encourage personal responsibility for safe behaviour

Safe behaviour can prevent more travel-related illness and deaths than specific vaccines and prophylactic drugs, important as these are. Personal responsibility should be encouraged. Emphasise health promotion, illness prevention, and appropriate care of illness or injury should it occur.

Although it is common and tempting for doctors to focus on immunisations and medication, spending time discussing safe behaviour is a critical part of good travel medicine practice.

As in other areas of patient education and behaviour change, the following elements are vital to promoting risk reduction through safe behaviour:

- sufficient knowledge of risks and of the means to minimise them
- personalisation of risks

- responsibility for minimising the risk to which one exposes oneself and others
- understanding that controlling behaviour will make a difference
  - being safe consistently (for example, wearing seat belts all the time, ensuring every sexual contact is safe).

The key areas for safe behaviour that require education of the traveller include:

- advice regarding safe food and drink
- insect avoidance
- environmental and animal exposures
- substance abuse
- sexual encounters
- injury
- blood-borne infections.

Many of these issues and how to avoid potential disease exposure are discussed further in subsequent chapters, but will be briefly addressed here.

Food and drink

Eating and drinking safely to minimise the risk of enteric infections is discussed in detail in Chapter 4, Travellers' diarrhoea. While these measures are technically correct and effective if applied consistently and rigorously, the difficulties in their consistent application are considerable. One classic study of Swiss travellers found that 98% had transgressed one or more dietary guidelines of which they had been informed within 48 hours of arriving in Kenya or Sri Lanka.

Insects

Many infectious diseases are transmitted by biting insects, mostly mosquitoes, but also by a large variety of others, including ticks, mites, flies, fleas, sandflies, lice and triatomine bugs. Although these insects differ widely in their ecology and biting habits, the same preventive measures are effective against virtually all of them: sleeping in screened accommodation or under a mosquito net, preferably permethrin impregnated; covering up with long sleeves and long pants (especially after dark); and applying DEET-containing repellent on bare skin. Permethrin impregnation of clothing and bed sheets is an additional protective measure. See Chapter 3, Malaria prevention, for more information on DEET and permethrin.

Environmental exposures

Travellers should avoid walking with bare feet, and should instead wear sandals or sneakers because some parasites enter the body through skin contact with contaminated soil. Tourists should avoid swimming in beaches that might be

contaminated with human sewage or with dog faeces, as this can be a source of many infections.

Swimming, wading or canoeing in fresh water may be a source of infections, including schistosomiasis and leptospirosis. Thus, it is advisable for travellers to areas where these infections are endemic to avoid contact with bodies of fresh water.

Exposure to soil, excavations and caves may also be a source of endemic fungal infections; whenever possible, tourists should avoid dust exposure in contaminated areas.

Animal bites

All travellers, especially those going to rabies-endemic areas, should be aware of the importance of avoiding animal bites or scratches. Engaging in feeding, patting, playing with, or any other interaction with animals, should be minimised. Risks can include camel bites while riding them! All wounds should be cleaned immediately and dressed appropriately to prevent secondary infection, and some (e.g. dog and cat bites) may need prophylactic antibiotics.

Additional preventive advice for travellers to areas with rabies includes:

- appropriate care for possible exposure to rabies – immediately wash wound or saliva-contaminated mucous membrane thoroughly with copious water and soap, and apply an antiseptic such as iodine
- medical consultation regarding post-exposure rabies prophylaxis (PEP) should be given as soon as possible, preferably within 48 hours.

Returned travellers commonly present for rabies PEP days, weeks or occasionally months after a rabies-prone bite. PEP is indicated irrespective of how long it has been since the bite, but its efficacy declines with time elapsed beyond 48 hours after the possible exposure.

Optimally, more pre-exposure rabies vaccination should be administered, but the limiting factor is its high cost. Children in particular should be targeted for pre-travel rabies vaccination, as they are more likely to interact with animals and less likely to report if a scratch or bite has occurred (see chapter 2.13).

Substance abuse

Travel, particularly for holidays, to an environment where anonymity is likely, is often associated with a sense of freedom from the usual social, work-related, family and cultural constraints. This, combined with a variety of often appealing and inexpensive temptations, produces increased risk-taking behaviour by many travellers. This occurs particularly in relation to sex, substance abuse, and activities involving risk of injury.

Alcohol and marijuana abuse are associated with an increased risk of injury and unsafe sex, and injecting drugs may pose significant risk of infections. Expatriates are at risk of alcohol abuse, particularly in tropical environments where alcohol is cheap, socially acceptable, and readily available, and where social outlets are limited.

Sex

Studies show that the vast majority of long-term travellers and expatriates are sexually active during their trip. Of short-term travellers, 5% engage in casual sex and 20% of short-term male travellers travelling alone engage in casual sex during their travel. There are differences in sexual partners between the sexes – female travellers tend to have sex with other travellers; male travellers tend to have sex with locals. Studies of sexual behaviour during travel consistently indicate that only 30–50% of casual travel sex is protected.

Thus, the safety of sex should be a routine issue for discussion during the travel health consultation. Condoms should be carried by travellers on the basis of possibility, not intent, so that they are readily on hand if needed and are of reliable quality.

In the case of sexual assault or unsafe consensual sex, especially in areas where HIV is highly endemic, travellers should be educated that post-exposure prophylaxis is increasingly available to prevent HIV infection, and therefore they need to seek medical attention urgently to address this issue (preferably within 12 hours, as this is when it will be most effective, but prophylaxis may be given up to 72 hours post exposure).

Oral contraceptive pill

Travellers taking the oral contraceptive pill should be aware that it may be ineffective or have decreased efficacy in the presence of diarrhoea, vomiting, or certain antibiotics.

Time zone changes may complicate pill-taking time. The easiest way to manage the oral contraceptive pill during travel is to keep a watch on 'home' time and take the pill at the usual home time. If this pill-taking time is inconvenient, adjust it by about four hours earlier or later each day until a suitable local time is reached. If in doubt, take the pill earlier rather than later. Advise travellers never to be more than 12 hours late taking the pill.

Injury

Traffic accidents

The most common cause of travel-related death is trauma, mostly related to traffic accidents. In most developing countries, the accident rate per kilometre

is substantially higher than in Australia. Vehicles and tyres are often poorly maintained; seat belts are often missing or of poor quality; roads are often poorly maintained, poorly lit and crowded with people and animals; and road rules are often not well observed. In addition, travellers often take risks they would never contemplate in Australia (for example, not wearing seat belts, riding motorcycles without appropriate training, helmet and protective clothing, drinking and driving, and riding in the back of open vehicles). The highest risk is associated with motorcycles, and travellers should be discouraged from using them.

Not only are the risks of a crash-related injury increased when travelling in developing countries, but the consequences of an injury may be greater. Good emergency medical care may be difficult or impossible to obtain locally, and considerable delays may occur. An injury that may not be serious with good emergency care may become serious when care is delayed. For travellers, avoidance of trauma is the most important way to minimise the possible need for blood transfusion. Finally, there are often significant risks of personal injury from bystander violence following accidents.

Travellers should:

- check the condition of vehicles they travel in, particularly brakes, tyres and lights
- ensure seat belts are fitted, functional, and worn at all times
- avoid driving at night
- avoid excessive speed
- not drink and drive
- avoid motorcycles or, if this is not possible, travellers should ensure they are experienced riders and have a high-standard helmet and protective clothing.

Aquatic injury

The second most common cause of life-threatening injury in travellers is aquatic injury, including drowning. This often relates to travellers being unfamiliar with local conditions, overestimating their capabilities, or undertaking aquatic activities while intoxicated.

Assaults

Expatriates and travellers may have concerns about the risk of being assaulted. Assault can have severe and persistent physical and mental consequences, particularly if it has a sexual element, and is an important health issue.

- Advise travellers not to walk alone in remote areas, back streets or beaches, where there may be risk of personal attack.

- Valuables, passports, tickets, and money should be left at home or deposited in hotel safes, and a money belt should be used for essential items.

Blood-borne infections

Hospitalisation for any type of injury may be associated with a significant risk of nosocomial infection, in part through blood transfusion. Most developing countries screen donated blood for HIV and hepatitis B, but this may not be consistently or reliably performed. In addition, few developing countries screen for hepatitis C (with an estimated global prevalence of 3%). In some countries, screening for malaria, syphilis, and trypanosomiasis may also be relevant.

Blood-borne infections also pose a risk during other medical and dental procedures, injecting drug use, contact sports, first aid, health-care work, tattooing, acupuncture, close social contact, scarification, and any other skin-piercing activity. This is particularly the case for hepatitis B, the most contagious blood-borne virus. Those likely to be involved in any of the above should be vaccinated against hepatitis B.

The World Health Organization estimates that about half of the 10–15 billion injections given annually worldwide are unsafe. While travellers will generally be treated with the best resources available locally, safety of procedures and quality of infection control practice cannot be assumed. Elective surgery, dental work, and childbirth should preferably be undertaken under optimal conditions.

Travellers should enquire and reassure themselves about the sterility of instruments and equipment used for any procedure they undergo, particularly in resource-limited environments. Often travellers can ask to see a new needle and syringe being removed from their packaging. For long-term travellers and expatriates in remote and resource-limited areas, a comprehensive medical kit, including items such as needles and syringes, suture material, intravenous cannulae, and giving sets can be carried.

The risks of nosocomial blood-borne infection can be minimised if travellers are up-to-date with routine screening tests and any clinically indicated measures, by having a dental check before travel and, for long-term travellers and expatriates, having a comprehensive pre-departure medical examination. Whenever possible, oral medication should be used in preference to injectables in settings where infection-control practice is dubious.

For those at significant risk of HIV exposure (e.g. health-care workers in areas with high HIV endemicity), carrying a post-exposure prophylaxis antiretroviral starter pack is strongly recommended in case of potential HIV exposures. Specific advice regarding drug regimen and indications should be sought from medical practitioners experienced in HIV care. The cost of the medication

will not be covered under the PBS and will need to be borne by the individual or the employer.

1.8 Consider costs

Pre-travel health advice, with comprehensive immunisations and malaria prophylaxis, may not be cheap. For example, a long-term expatriate being posted to Africa may require up-to-date immunisations against diphtheria and tetanus, polio, hepatitis A and B, yellow fever, typhoid, meningococcal disease, rabies, measles-mumps-rubella, and BCG (total cost may be over $600), as well as anti-malarial prophylaxis (an additional $250 or so per year). Responsible employers will cover these and other health costs.

However, many individual travellers have limited budgets and do not expect to pay the high prices required for comprehensive pre-travel prophylaxis. For most travellers, the cost of health preparations is a minor component of the total cost of their trip, which is rarely less than several thousand dollars. Most immunisations provide protection over at least a few years; some, such as diphtheria/tetanus, polio, and yellow fever require boosters only every 10 years; hepatitis A and B vaccines provide life-long protection; others, such as BCG, need not be repeated for adults. Thus, they should be regarded as a long-term investment in health, providing protection not only for the current trip but also for future trips.

Convincing travellers of the benefits of indicated health preparations, and helping them choose the most useful interventions within a restricted budget, are an inevitable part of the travel health adviser's role. At a minimum, most travellers should be vaccinated against diphtheria/tetanus, polio, and hepatitis A. Travel health providers should be familiar with the costs of items they prescribe.

Some vaccines, such as rabies and Japanese encephalitis, are much more expensive in Australia than in many other countries ($80–$100 per dose compared with often <$20 per dose). As they are usually indicated for long-term travellers and expatriates, a reasonable cost-saving option is for travellers to have these vaccines soon after their arrival overseas, if quality services are available there.

1.9 Provide written information

Patients have limited retention of voluminous, complex information given during consultations. Much of the information about risk avoidance, illness, and care provided at the pre-travel consultation may not be relevant until many months later. Before travel, people are often busy, with much to organise and finalise, yet information about a whole range of issues may be important.

It is therefore essential to provide written information that travellers can take with them to read later and even carry on their travels. A variety of information sheets, pamphlets, and books are available. A selection of these should be available at any clinic providing pre-travel health advice.

1.10 Recommend a medical kit

A medical kit is appropriate for almost all travellers, even those visiting low risk destinations. This may vary from bandaids, condoms, and paracetamol for a short trip to Europe, to splints, stretcher, intravenous fluids and giving sets, emergency drugs, an oxygen supply, endotracheal tubes, and ventilation equipment for a mountaineering expedition.

As well as having commonly needed items of known efficacy on hand immediately, a medical kit provides a reminder of important health issues, and requires personal responsibility to compile or obtain it.

A checklist for medical kits that are not highly specialised is given below. For many travellers, buying a medical kit will be more practical than compiling one themselves.

1.11 Recommend health insurance

Health insurance should be recommended to protect travellers against the expense of medical, hospital, and pathology bills they may incur if they require medical care while overseas. Additionally, health insurance will provide access to emergency medical assistance if required. Most travel insurance packages cover emergency medical care and advice, and allow emergency medical evacuation involving a dedicated aircraft and medical team if necessary. Without insurance, this could cost individuals well over $100 000. If patients have chronic or intercurrent illness prior to travel, it is important to ensure that treatment of these conditions will be covered if required during travel.

The Australian Federation of Travel Agents recommends that travel agents routinely suggest travel health insurance to their clients.

If they become ill while overseas, travellers should:

- document any illnesses, doctor visits, and medications received
- keep accounts from doctors, hospitals, and pharmacies
- ask for a letter from the doctor who treats them overseas that outlines the problem, the investigations performed, the results, the diagnosis, and the treatment given.

Medical kit checklist for travellers

1. Documentation

[ ] Immunisation record (essential if yellow fever or meningococcal immunisation required)

[ ] Doctor's letter detailing chronic conditions, status, complications, treatment, recent test results, contact details

[ ] Bracelet or similar device containing details for potential emergency issues

2. First-aid items

[ ] Adhesive dressings, sterile gauze, bandages, tape

[ ] Scissors, tweezers

[ ] Eye pad

[ ] Iodine solution (antiseptic plus water disinfectant), sterile saline

[ ] Gloves

[ ] Needles/syringes/IV cannulae

3. Illness care

[ ] Aspirin/paracetamol, stronger analgesic if going to remote areas or areas posing a high risk of injury

[ ] Diarrhoea kit

Oral rehydration solution (especially young children)

Quinolone or macrolide antibiotic

Thermometer

Tinidazole, especially if travel is prolonged and to remote areas

[ ] Anti-emetic

[ ] Malaria emergency self-treatment

[ ] Anti-histamine or other anti-allergy medication

[ ] Steroid cream

[ ] Other commonly required medications, e.g. for thrush

4. Preventive care

[ ] DEET-containing insect repellent

[ ] Permethrin to impregnate bed nets, clothing

[ ] Antimalarial drug (prophylaxis)

[ ] Sunscreen (SPF 15+)

[ ] Immersion heater, filter and/or iodine solution to disinfect drinking water

[ ] Condoms

[ ] Decongestant (for air travel with hay fever or cold)

[ ] HIV PEP starter pack (if appropriate)

5. Usual care

[ ] Usual medication (ample quantities, carry in hand luggage)

[ ] Usual health monitoring equipment (e.g. blood glucose monitor, fingerprick device and testing strips, peak expiratory flow meter)

[ ] Spare pair of glasses or contact lenses and solutions, optical prescription

6. Miscellaneous

[ ] Short–medium acting hypnotic (e.g. oxazepam)

Steps during consultation

These will vary depending on the traveller, the trip, the doctor, how well the traveller is known to the doctor, and previous travel health care.

A general checklist

- Review traveller's completed pre-travel form outlining date of departure, details of the planned trip, past medical and immunisation history (with dates), drug allergies, antimalarial drug experience, current medications and actual, possible or planned pregnancy.
- Find out how definite the itinerary is and the range of possible variations.
- Discuss any particular implications for the planned travel of medical history, conditions, or treatment.
- Determine particular risks, current epidemics, yellow fever immunisation requirements, and malaria situation in areas to be visited.
- Review immunisation history and vaccine checklist to discuss and agree on an immunisation plan (receptionist should have previously explained the likely cost of the consultation, vaccines and medication).
- Discuss and agree on malaria prophylaxis (including protection against insect bites).
- Discuss prevention and management of diarrhoea.
- Address traveller's questions and concerns.
- Discuss any other issues, including injury, rabies, schistosomiasis, sex, HIV, and health insurance.
- Provide/review written information.
- Complete the traveller's immunisation record (yellow WHO International Certificates of Vaccination booklet) – keep a copy in the patient file; preferably include vaccine batch numbers in both records.
- Write prescription for remaining items.

We usually give vaccines at the end of the consultation. An experienced nurse and pharmacist can provide valuable assistance and contribute to patient education.

Key readings

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Chapter 2

Immunisation

Chapter outline

2.1 Introduction to pre-travel vaccination

Vaccine choice and priorities should be individualised – 'this traveller, this trip, this time' – and will vary depending on characteristics of the patient (prior vaccination status, disease history, immune status, age, chronic conditions, etc.) as well as on destination, duration, type of travel and activities, likely exposures, and the range of likely possibilities for these. It may be perfectly appropriate to

recommend different vaccines, and other measures, for two people going on the same trip. It may be just as important to understand the range of potential variations on a planned trip as to be aware of the current plans. How risk-averse the travellers are and their willingness to invest in prevention are also important considerations.

It can be as important to understand what travellers might do as what they plan to do.

Categories of vaccines

We find it useful to consider vaccines in three categories: required, recommended, and routine. Some general points may help decide which vaccines are most important.

Required

- **Yellow fever (YF) vaccine**: This is the only mandatory immunisation authorised by the current International Health Regulations (2005). Yellow fever vaccine is given for two overlapping but distinct reasons. Many countries considered vulnerable to YF importation require YF immunisation as a condition of entry for travellers who arrive from (even following only airport transit in) a yellow fever endemic country. These requirements are subject to change; those advising travellers should check current information, available at <www.who.int/ith>. The lack of a mandatory government requirement for travellers of immunisation against YF does not necessarily mean that there is no risk of YF in that country.

  YF immunisation is medically indicated for protection of travellers visiting areas with a risk of YF transmission, even if there is no requirement for travellers to that place to be immunised.

- **Meningococcal vaccine**: A valid certificate of tetravalent meningococcal vaccination is currently required by Saudi Arabian authorities for pilgrims attending the annual Hajj pilgrimage or for the Umrah (a different form of pilgrimage to Mecca which can be undertaken at any time of year), and for seasonal workers and residents of Mecca and Medina.

- **Requirements for travellers including pilgrims to Saudi Arabia**: The annual Hajj is the largest regular international mass movement of people, bringing millions of people from all over the world in close proximity for a few weeks. Not surprisingly, it has been the setting for transmission and outbreaks of a range of infectious diseases, including meningococcal disease and influenza. Vaccine requirements for Hajj pilgrims and other travellers are issued each year by the Ministry of Health of Saudi Arabia, and published in the WHO Weekly Epidemiological Record <www.who.int/wer>. These vary from year to year and the most recent requirements should be referred to. However it is likely that the requirements related to meningococcal disease, polio and yellow fever will continue for the foreseeable

future. By way of example, for the 2009 Hajj and Umrah seasons, immunisations requirements were as follows (WHO 2010):

  - *Yellow Fever*: travellers from countries or areas at risk of yellow fever transmission must present a valid YF immunisation certificate.
  - *Meningococcal disease*: meningococcal ACYW135 immunisation at least 10 days before entry but within the previous 3 years is required of all pilgrims and seasonal workers over 2 years of age. In addition, those arriving from countries in the African meningitis belt are given chemoprophylaxis (ciprofloxacin for most adults, rifampicin for children, and cetriaxone injections for pregnant women) on arrival.
  - *Polio*: all visitors arriving from countries endemic for or re-infected with polio should have received a dose of polio vaccine (OPV is specified) at least 6 weeks prior to departure for Saudi Arabia; and all arriving visitors from polio-endemic countries (Afghanistan, India, Nepal and Pakistan) will also be given a dose of OPV at entry points to Saudi Arabia.
  - *Influenza*: seasonal vaccine is recommended especially for those with pre-existing conditions.
  - *Routine vaccines*: Saudi authorities strongly recommend pilgims be up-to-date with routine immunisations like tetanus, diphtheria and measles.
- Cholera immunisation is not a requirement of entry to any country.

Consider not only which vaccines are appropriate for this trip, but which ones would be appropriate for likely travel over the duration of protection of the vaccine.

Recommended

Being up-to-date with changing epidemiology and current outbreaks helps to prioritise pre-travel immunisations. Changes can be particularly dramatic for influenza, meningococcal disease, and cholera, but can occur with almost any infectious disease.

- **Hepatitis A** is generally the second most common vaccine-preventable disease in travellers. The vaccine is extremely effective, well-tolerated, and provides long-lasting immunity. It should be recommended for all travellers not known to be immune who are going, even for a short time, to areas where sanitation and hygiene are suboptimal.
- **Influenza** is the most common vaccine-preventable disease in travellers. Both seasonal and pandemic vaccine should be strongly considered, particularly if travel coincides with the influenza season, if travel is in large groups and confined surroundings like cruise ships, or if the traveller has any risk factors for severe influenza.
- **Typhoid** immunisation should be targeted to those at high risk according to the destination (especially South and South-East Asia, North and West

Africa, impoverished areas of Latin America, and Pacific Island countries including Papua New Guinea), duration (anticipated risk period of 2–3 weeks or more, or repeated travel expected over the duration of efficacy of the vaccine – 3 years for injectable vaccine, and 5 years for oral vaccine), and type of intended travel (with high likelihood of enteric exposures). Immigrants returning home and their children make up a disproportionately high fraction of typhoid cases.

- **Rabies, Japanese encephalitis (JE), BCG, cholera and tick-borne encephalitis** vaccines are generally reserved for travellers with the potential for specific (for example occupational or recreational) or prolonged exposures. Evidence that rabies vaccine boosters are not needed in immunocompetent persons (WHO and CDC recommendation; see the discussion of boosters in chapter 2.13, Rabies) and the advent of new highly purified, less reactogenic and probably longer-lasting JE vaccines should lead to both rabies and JE vaccines being used more widely for travellers, particularly those likely to travel repeatedly. The partial protection offered by the inactivated oral cholera vaccine against enterotoxigenic *E coli*, the commonest cause of travellers' diarrhoea, means that this vaccine has a benefit in addition to cholera protection, of a likely average 10–20% reduction in the incidence of travellers' diarrhoea. While this is a relatively small efficacy and travellers' diarrhoea is rarely serious, the high frequency of travellers' diarrhoea means that this represents a relatively large number of cases potentially prevented.

Individual protection is not the only benefit of or reason to use travel vaccines – many have important public health benefits and reduce potential transmissibility to others, both during travel and on return home. This includes measles, polio, influenza and hepatitis A. Many immunisations given in the context of travel also confer ongoing protection relevant at home, e.g. immunisation against influenza, hepatitis A and B, and rabies (protective against Australian bat lyssavirus).

It must be emphasised that while immunisation is important, a high proportion of travel-related illness and injury is preventable only by safe behaviour, such as protection against mosquitoes and other insects, food and water hygiene, safe-sex practices, and injury prevention. Hence, education and encouragement regarding safe behaviour must not be neglected in the pre-travel consultation. Practice staff, particularly practice nurses, have an important role in both immunisation and health education of travellers.

Routine

The pre-travel consultation provides an ideal opportunity to ensure that patients, both paediatric and adult, are up to date with standard vaccines recommended irrespective of travel. Vaccine schedules in children should be continued uninterrupted whenever possible, and may warrant acceleration. Travel

may increase exposure to most vaccine-preventable diseases and hence the importance of timely administration of routine vaccines.

Travellers may also themselves become vectors of disease, and can bring home and then transmit to their contacts vaccine-preventable diseases such as measles, polio, influenza, meningococcal disease, diphtheria, and hepatitis A and B. Outbreaks of vaccine-preventable diseases like measles, pertussis, diphtheria, and meningococcal disease make up-to-date routine immunisation even more important for travellers to affected regions.

All health professionals who advise travellers should be familiar with and promote the current National Immunisation Program Schedule. At time of writing, this was the version issued in July 2007, described in detail in the *Australian*

Table 2.1.1 Australian Standard Vaccination Schedule, 2007

Age	Vaccine											
Birth	Hepatitis B*											
2 months	Hepatitis B*	DTP_a	Hib[1]	IPV			13vPCV		Rotavirus			
4 months	Hepatitis B*	DTP_a	Hib[1]	IPV			13vPCV		Rotavirus			
6 months	Hepatitis B*	DTP_a	Hib[1]	IPV			13vPCV		Rotavirus[3]			
12 months	Hepatitis B*		Hib[1]		MMR			MenCCV			Hepatitis A[4]	
18 months						VZV	13vPCV/ 23vPPV[2]					
2 years												
4 years		DTP_a		IPV	MMR		23vPPV					
10–13 years	Hepatitis B course					VZV				HPV (girls)		
15–17 years		dTpa										
15–49 years							23vPPV					Influenza (annual)
50 years and over							23vPPV					Influenza (annual)
65 years and over							23vPPV					Influenza (annual)

Note: Vaccines currently funded under the National Immunisation Program are shaded.
Vaccines lightly shaded are funded for targeted, at-risk populations only.
* Following the birth dose, 3 further doses of hepatitis B vaccine are required at either 2, 4 and 6 months, or at 2, 4 and 12 months.
1 For PRP-T Hib vaccines, 4 doses are given at 2, 4, 6 or 12 months. For PRP-OMP Hib vaccines, 3 doses are given at 2, 4 and 12 months.
2 Children with underlying medical conditions should receive 13vPCV at 2, 4, 6 and 12 months. Aboriginal and Torres Strait Islander children living in NT, Q, SA and WA should receive 13vPCV at 2, 4 and 6 months, and 23vPPV at 18–24 months. Both groups should then receive 23vPPV at 4–5 years.
3 Third dose required for Rotataq but not for Rotarix.
4 Two doses of hepatitis A vaccine for Aboriginal and Torres Strait Islander children, commencing in the 2nd year of life.

Immunisation Handbook 9th edition (Jan 2008). Between print editions (the 10th edition is expected in 2012), the electronic version of the handbook is periodically updated. Both the handbook and updates are available at <www.immunise.health.gov.au>. Providers can also register to be sent email information about handbook updates when they are issued.

Delay in vaccine doses

A delay in completion of primary doses or an excessive delay in booster doses does not mean the schedule needs to be restarted. The missing doses should simply be completed at recommended intervals; no 'backtracking' is needed. The simple rule is: every vaccine dose counts (as long as the recommended doses of potent vaccine have been given at not less than the minimum recommended intervals above the minimum recommended age). This is because of the power of immune memory. The only exceptions are the oral typhoid vaccine, for which an interrupted course generally warrants re-starting the course or using the injectable vaccine instead (see chapter 2.17, Typhoid), and the inactivated cholera vaccine, for which NHMRC and CDC recommend that the first dose should be repeated if the second dose has not been given within 6 weeks of the first.

Simultaneous administration of different vaccines

There is no contraindication to simultaneous administration of any vaccines.

Most vaccines can be administered simultaneously at different sites (at least 2 cm apart) without impairing immune responses or increasing adverse events. Giving as many vaccines as practical at the same time helps ensure that they are received and in time, simplifies pre-travel preparation, and minimises the number of clinic visits.

Inactivated vaccines can be given at any time in relation to live or other inactivated vaccines, or tuberculin (Mantoux) testing.

For injectable live viral vaccines (or the intranasal live attenuated influenza vaccine licensed in the United States and Europe but not available in Australia at time of writing), the immune response to one live virus vaccine might be impaired if administered within 28 days of another injectable live virus vaccine. For example, the risk of breakthrough varicella is increased if varicella vaccine is given <30 days after MMR. Thus parenterally administered live vaccines should be administered either simultaneously or at least 4 weeks apart whenever possible. (An exception is yellow fever given after monovalent measles, where interference has been shown not to occur.)

Oral typhoid vaccine (as for oral polio vaccine in the past) can be given at any time in relation to any other vaccine, except that the NHMRC recommends that

Table 2.1.2 Spacing of different vaccines and immunoglobulin

Vaccines	Simultaneous administration permissible	Suggested interval if not given concurrently
Inactivated vaccines	• All other inactivated vaccines • All live vaccines (except inactivated oral cholera vaccine should be given ≥8 hours apart from oral live attenuated Ty21(a typhoid vaccine))	• All other vaccines – any interval before or after each other
Yellow fever	• MMR, MMRV, rubella • Smallpox • Oral typhoid – Ty21a • Oral cholera • OPV	• MMR, varicella, rubella – 4 weeks apart • OPV – no interval required
Cholera– oral inactivated (WC-rBS)	• Any inactivated vaccines • Any live vaccines except Ty21a	• Ty21a – separate by ≥8 hours
Oral typhoid – Ty21a	• All live and inactivated vaccines • Immunoglobulin	• Oral cholera – separate by ≥8 hours • Yellow fever, MMR – no interval required • OPV – if feasible 2 weeks before or after Ty21a, otherwise no interval required
MMR	• All live and inactivated vaccines	• Yellow fever, varicella – 4 weeks apart
Varicella	• All live or inactivated vaccines	• MMR, yellow fever – 4 weeks apart • OPV – no interval required
BCG	• OPV • Immunoglobulin	• OPV – no interval required • Other live vaccines – 3 weeks apart
Immunoglobulin	• Yellow fever • OPV • Inactivated vaccines at different sites	• MMR, varicella – at least 3 weeks before, or 3–6* months after IG • Yellow fever, Ty21a, OPV – no interval required
Oral polio vaccine (OPV)	• All live vaccines • Ty21a • Immunoglobulin	• Ty21a – if feasible 2 weeks before or after OPV • MMR, yellow fever, varicella, BCG – no interval required

* dose-dependent

there should be an interval of ≥8 hours between administration of oral inactivated cholera and typhoid vaccines, as the the buffer used in the cholera vaccine might affect the gut transit of the attenuated bacteria in the oral typhoid vaccine.

Interaction between vaccines and tuberculin skin test

Tuberculin (Mantoux) testing should be done at the same time as parenteral live virus vaccines (especially MMR), or delayed by 4–6 weeks, as these

vaccines may transiently suppress the response to tuberculin testing. This does not apply to live oral vaccines such as OPV, oral typhoid or oral cholera vaccines, or presumably rotavirus vaccines.

Interaction between vaccines and antimalarials

As discussed in detail in chapter 2.17, Typhoid, recommendations on antimalarials in relation to Ty21a oral typhoid vaccine are conflicting, in the face of an incomplete evidence base. We therefore recommend a cautious approach – that antimalarials other than chloroquine should be avoided for 3 days before or after oral typhoid vaccine.

Interaction between vaccines and blood products

For some vaccines, circulating antibody to a vaccine antigen may interfere with the immune response to the same antigen present in a vaccine. The extent of interference depends on the type of vaccine and the amount of antibody. Inactivated vaccines are generally not substantially affected by circulating antibody, and simultaneous active and passive immunisation through immunoglobulin and vaccine administration is recommended for post-exposure prophylaxis for a variety of diseases, such as tetanus, hepatitis B and rabies. Simultaneous administration of immunoglobulin and hepatitis A vaccine (now recommended only for immunocompromised persons) does not affect seroconversion rates, but it reduces antibody titres achieved by about 50%. Whether this is of any clinical relevance is not known.

Interference is more likely with live vaccines, which usually replicate in order to stimulate an optimal immune response. Interference is less likely for live vaccines against diseases for which there is little or no circulating antibody present in the blood (or plasma) donor population, or for antibody-containing preparations that are highly specific (e.g. palivizumab, a humanised mouse monoclonal antibody to respiratory syncytial virus, which is produced in cultured cells and contains no other antibodies).

In general, no effect on the immune response to a vaccine will occur if an antibody-containing blood product is given ≥2 weeks later. If a shorter interval is necessary, the immune response to the vaccine should be checked or the vaccine dose should later be repeated.

The recommended interval between administration of a blood product and the subsequent administration of the live parenteral vaccines MMR, rubella and varicella depends on the amount of antibody in the blood product used. The US Advisory Committee on Immunization Practices (ACIP, CDC 2010) and NHMRC 2008 recommend intervals ranging between 3 and 11 months,

depending on the nature and dose of the blood product. The recommended intervals are 6 months for whole blood, 5 months for packed red cells, 3 months for red cells with adenine-saline added, and no interval for washed red cells. The recommended intervals following immunoglobulins (IG) vary from 3 months for tetanus and hepatitis B IGs and normal human IG for hepatitis A prevention, to 4 months for rabies IG, 5 months for varicella IG, and 6 months for CMV IG. Following intravenous IG, the recommended interval ranges between 8 and 11 months depending on the dose.

Anti Rh(D) immunoglobulin does not interfere with the immune response to rubella, MMR, varicella (or MMRV) vaccines.

Yellow fever, oral typhoid, oral cholera, and OPV vaccines can be given at any time in relation to blood products.

Interchangeability of vaccine products

While vaccines are not all the same, and immunogenicity, safety, and efficacy data on interchanging different vaccines at different time-points is far from complete, there is a substantial body of evidence supporting a generally high degree of interchangeability of vaccines of differing types and from different manufacturers. This is most clear cut and helpful where an established correlate of protection following immunisation is widely agreed, for example for hepatitis B, diphtheria, tetanus, and rabies.

Available evidence indicates that for the following diseases the available vaccines can be used interchangeably: tetanus, diphtheria, polio (OPV and IPV), hepatitis A, rabies, MMR, influenza, and Hib (although three doses in total are required with an all PRP-OMP schedule, four doses for any other Hib vaccine or combination of vaccines). Different brands of meningococcal and typhoid Vi polysaccharide vaccines can be used interchangeably for repeat immunisation.

Hepatitis B vaccines are interchangeable, except that the higher antigen Engerix B vaccine may perform better in those with reduced immunity, the elderly, or if the course is not completed.

For pertussis vaccines there is not an established correlate of protection and data on mixed schedules is limited, so it is recommended that, if possible, the same vaccine be used for the first three doses.

There are no firm data on interchangeability of different rotavirus, pneumococcal conjugate, HPV, or Japanese encephalitis vaccines. For varicella vaccines, while data and recommendations on interchangeability are lacking, both vaccines available in Australia utilise the same virus strain. For vaccines where interchangeability is not supported by sound data and clear recommendations, we recommend that if possible the same vaccine preparation be used to complete a course, but that immunisation providers should use whichever

preparation they have available if the vaccine used for previous doses is unknown or unavailable. We are not aware of any safety issues associated with use of different vaccine preparations, and do not believe immunisation should be withheld because the preparation available is or may not be the same as one used previously.

For the majority of vaccines, there is no increase in adverse events and no known disadvantage from immunising someone already immune to the disease, apart from the usually mild discomfort and cost of an unnecessary immunisation. This discomfort is usually far outweighed by the advantage of ensuring protection. For some vaccines, for example tetanus (marked local reactions often associated with high antibody levels) and human diploid cell rabies vaccines, the likelihood of adverse events increases with repeated booster doses, but in these situations the immunisation history is usually known. For some vaccines, successive doses are associated with a reduced likelihood of adverse reactions, for example the second dose of varicella vaccine in adolescents and adults.

The only vaccine for which it is important to evaluate immune status in every patient prior to immunisation (by skin and serum antibody testing) is Q fever, for which previous (potentially unrecognised) infection substantially increases the likelihood of hypersensitivity reactions to the vaccine.

Pre-immunisation tuberculin testing is recommended before administration of BCG vaccine, except for infants under 6 months of age (although the need for this has been questioned; see chapter 2.16, Tuberculosis).

Practical aspects of immunisation

- If possible, travellers should be encouraged to seek advice at least 6 weeks before travel. This enables a primary schedule (accelerated HB +/– HA, rabies, JE) to be completed for essentially all travel vaccines; allows time for indicated tests to be performed, reviewed and if necessary acted upon; generally allows immunisation to be completed about 2 weeks before travel, sufficient time for a protective immune response to have developed for most vaccines; and minimises the possibility of vaccine-related adverse events occurring during travel.
- The standard vaccination procedures described in *The Australian Immunisation Handbook* (9th edition, 2008) and updates should routinely be followed for all immunisations. These include having available at all times equipment and adrenaline to manage anaphylaxis, obtaining informed consent, checking the condition and expiry date of all vaccines administered, and observing vaccinees for at least 15 minutes after immunisation.
- Maintenance of vaccines under optimal conditions through competent and careful cold chain management is key to delivery of potent vaccines.

An approach to pre-travel immunisation

1. With what routine immunisations should this patient be up-to-date?

   For example:

   – hepatitis B and meningococcal C for a young adult

   – HPV vaccine for girls and young women

   – influenza and pneumococcal polysaccharide for an older person.

2. What additional immunisations should this patient be up-to-date with, in view of his/her medical history and individual factors?

   For example:

   – rubella, varicella, and pertussis for a woman considering pregnancy

   – HB, MMR, dTpa, VZ, BCG for a health-care worker

   – HA, MMR, VZ, dTpa, and HB for a childcare worker

   – influenza and pneumococcal polysaccharide vaccines for a person with chronic illness

   – HB and HA for men who have sex with men, and for those who inject drugs

   – rabies vaccine for vets, wildlife officers, and others in regular contact with bats

   – Q fever vaccine for farm and abattoir workers

3. What immunisations are indicated in this patient given his/her planned trip and likely future travel?

4. Are the details of the trip uncertain or subject to change? If so, should any additional immunisations be considered for now or during the trip?

5. Should this patient's immune status be checked (serologically) before or after immunisation?

   For example:

   – to establish immune status to MMR, VZ, HA, and HB in order to assess need for immunisation

   – to check response to immunisation following HB course for someone at ongoing occupational risk of exposure to blood-borne viruses, following an intradermal course of rabies vaccine, or in an immunocompromised patient.

6. Are there any potential vaccine interference and timing issues I should consider?

- The following information should be recorded in the patient's clinic record as well as in a patient-held (preferably lifelong) immunisation record:
  – name of vaccine and brand

  - batch number (particularly useful in the event of discovery of a problem with particular batches, whether safety or potency)
  - date, dose, route, and site of administration
  - name of person giving vaccine.
- Patients should be given a record of vaccine doses required to complete courses, and when boosters are indicated for vaccines with clear booster recommendations.
- Patients should be advised to make two photocopies of their immunisation record (like all other important travel documents such as passport front page, visas, travellers cheque serial numbers, insurance policy details, important medical documentation). One copy should be carried in their check-on luggage separate from the actual documents in their hand luggage, the other left at home where at least one reliable family member or friend knows where they are. Even if the immunisation record is not formally required en route, at least a copy, if not the original, should be carried. Leaving an electronic copy in one or two accessible places can also be of practical value.

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Bioterrorism

Human history is replete with instances of malevolent use of biological or toxic agents, but the likelihood of such an occurrence at any one time or place is very low. Even for those working in conflict zones or in locations considered at higher risk of terrorism, it is doubtful at time of writing that specific preventive measures against possible use of a biological weapon are warranted on any routine basis. The potential number of

agents that could be used in such a way is large, and it would be misleading and inappropriate to suggest that effective preventive or preparatory measures could realistically be taken against most of them by the majority of travellers. For many possible agents, the risk remains theoretical, and for a number of agents effective measures can be applied post-exposure.

We offer the following comments on selected possible biological weapons agents.

- Enteric infections such as polio, hepatitis A, typhoid, cholera, and *E coli*:
  - A potential additional advantage for immunisation against these; food, drink and personal hygiene; and travellers' capability to manage acute diarrhoea.
- Influenza:
  - A potential biological weapon; a strong case for wider use of seasonal and pandemic influenza vaccines among travellers already exists.
- Anthrax:
  - Vaccines are available internationally and were used for Australian Defence Force personnel in Iraq in 2003, but are not currently registered in Australia. Vaccine could, and probably ideally should, be added to antibiotic prophylaxis (ciprofloxacin or doxycycline) following exposure.
- Plague:
  - Production by CSL of the killed whole-cell vaccine has ceased and the vaccine is no longer available. Such vaccines are effective against bubonic but not pneumonic disease, which would be most likely following use of plague as a weapon. Antibiotics (doxycycline) should be used in the event of exposure to plague.
- Q fever:
  - Australia is the only country with a registered vaccine (recommended on the basis of occupational exposure to cattle, sheep, goats, kangaroos, or their products). Post-exposure immunisation does not prevent disease.
- Smallpox:
  - Immunisation is effective up to 7 days after exposure. A stockpile of vaccine is held in Australia for emergency use. The only current indication is for laboratory staff working with live pox viruses. The existence of virus stocks other than those in Atlanta, USA and Koltsovo, Russia is not publicly known at time of writing.

In summary, the potential risk of the use of biological weapons may strengthen the case for use of vaccines for which there is already a strong case, especially influenza, polio, hepatitis A, and typhoid vaccines; and cholera vaccine (for both cholera and enterotoxigenic *E coli* protection). We do not feel that any significant change in practice is warranted in general advice to travellers on the basis of potential use of biological weapons. Effective post-exposure prophylaxis is available for a number of potential biological weapons, and travellers with particular concerns should be made aware of this. Doxycycline, commonly used for malaria prophylaxis, is also effective for prophylaxis of a number of other infections, including anthrax, cholera and plague.

2.2 Cholera

Disease

Vibrio cholerae is a bacterial infection that causes profuse, watery diarrhoea. Although it may be life-threatening, most infections are asymptomatic or mild, and with proper rehydration therapy the mortality rate is <1%.

Epidemiology

The majority of cases worldwide are due to the O1 serogroup (Classical or El Tor). However, since 1992, a new epidemic of serogroup O139 ('Bengal') has occurred, beginning in Bangladesh and India, and spreading to now at least 11 countries in South and South-East Asia. This strain is not preventable by current vaccines.

The reported risk of acquiring cholera while travelling in affected areas (Map 1) is thought to be <1:500 000, or 0.001–0.01% per month of stay in a developing country. The reported rates in Japanese travellers are higher (13:100 000 travellers to Bali). This is thought to be mainly due to more intensive surveillance, the consumption of raw seafood, and a higher prevalence of atrophic gastritis. Each year there are 2 to 6 cases of cholera reported in Australia in individuals who have been infected during travel to Asia, Africa, the Middle East, or South America. During the first 20 years of the current seventh pandemic, only 10 cases of cholera were reported among US travellers. However, since 1991, when cholera became endemic in Latin America, the number of reported cases of cholera in the United States has increased, with 37 cases in travellers reported between 1995 and 2000. Most of these were not in tourists, but occurred in visitors to family, relatives, and friends in high-risk countries. All travellers who developed cholera after visiting South America had consumed high-risk food such as raw or undercooked seafood, or had drunk unboiled water.

Active surveillance studies of expatriates and travellers have identified a higher incidence of cholera than reported by routine passive surveillance systems. This under-recognition of cholera occurs because mild cholera is not clinically distinguishable from other causes of acute watery diarrhoea, most cases of acute travellers' diarrhoea are not investigated, and specialised culture media are required to grow the causal organism. However, since cholera responds well to standard treatment, and secondary transmission from travellers has not been described, this under-recognition is of little consequence.

Vaccine

Oral killed whole cell-B subunit vaccine (Dukoral)

This vaccine is composed of heat and formalin inactivated Inaba, Ogawa, Classic and El Tor strains of *V cholerae* O1 in combination with a recombinant cholera toxin B subunit (rCTB). Dukoral is distributed by Sanofi Pasteur.

Dosage and administration

- Two doses, 1–6 weeks apart. If the second dose is not administered within 6 weeks, re-start the vaccination.
- Children aged 2-6 years should receive three doses of vaccine. If an interval of more than 6 weeks occurs between any of the doses, re-start the vaccination.
- To be taken on an empty stomach (no food or drink 1 hour either side of dose) with a glass of water and an alkaline buffer.

Efficacy

The vaccine provides high-level (85%) protection against El Tor cholera for 6 months in children and adults. In persons >5 years of age, protection of 78% at 1 year and 72% at 3 years has been recorded, while in children aged 2 to 6 years the protective efficacy at the end of 1 year is 44% and by 2 years only 33%. In those <5 years, protection has fallen to zero by 3 years after immunisation. It is effective from 1 week after the second dose. It does not protect against the O139 serogroup *V cholerae*.

In vaccine efficacy trials, a 52% reduction in the incidence of diarrhoea caused by heat-labile toxin producing enterotoxigenic *Escherichia coli* (LT-ETEC) was noted as a secondary outcome in the vaccinated population. The duration of protection against LT-ETEC is relatively short-lived, lasting up to 3 months.

Boosters

If ongoing protection is required, a single dose should be given after 3 years for adults and children over 6 years of age, and 6 months for children 2 to 6 years of age.

Adverse effects

This vaccine is free of significant adverse effects.

Pregnancy

It is not recommended in pregnancy.

Interactions

The administration of WC/rBS vaccine must be separated from Ty21a by at least 8 hours. It can be safely given with other vaccines without altering the protective efficacy against cholera or of the co-administered vaccine.

Recommendations

There are now no countries that require cholera vaccination as a condition of entry. Due to the low risk of travellers acquiring cholera, the usually mild and self-limiting nature of the disease, and the low mortality if fluids are maintained, cholera vaccine is not recommended for routine travellers to cholera endemic regions.

Vaccination to reduce the risk of cholera is worthwhile for:

- humanitarian workers operating in an epidemic or refugee situation
- travellers, especially those visiting relatives and friends living in unhygienic conditions in cholera-endemic areas
- travellers visiting cholera-endemic areas, who have pre-existing conditions that may be aggravated by cholera – for example, inflammatory bowel disease and malabsorption
- travellers with achlorhydria visiting cholera endemic areas.

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2.3 Diphtheria and tetanus

Background and epidemiology: diphtheria

Diphtheria is an acute mainly upper respiratory infection that historically caused substantial mortality. However, widespread vaccination has led to its virtual disappearance. A major epidemic of diphtheria occurred in the former Soviet Union in 1990–98 as a result of disruption of vaccination programs. Cases occurred in neighbouring European countries, and a number of cases occurred in travellers to affected areas. Almost all cases in developed countries are now associated with imported infections.

Background and epidemiology: tetanus

Tetanus is a serious acute disease caused by a potent exotoxin produced by the soil-dwelling Gram-positive bacterium *Clostridium tetani*. Clinical syndromes are generalised (>80% of cases), localised and cephalic, with key features of muscle rigidity, spasms, and autonomic dysfunction. Even with modern intensive care management, the overall case fatality rate has not been reduced below 10%. Neonatal tetanus is the most common form worldwide, typically as a result of umbilical stump infection. As a result of maternal and neonatal tetanus elimination efforts coordinated by WHO, emphasising clean delivery and immunisation of women of child-bearing age, the number of maternal and neonatal deaths has dropped dramatically.

In Australia, fewer than 20 cases are reported per year, mostly in older adults who have never been adequately immunised, or who have neglected to maintain immunity through boosters. The injuries implicated are typically minor,

often penetrating, wounds incurred while gardening, particularly involving thorns, and for which medical care was generally not sought.

Diphtheria- and tetanus-containing vaccines

- DTPa refers to child formulations of diphtheria, tetanus, and acellular pertussis-containing vaccines.
- dTpa refers to formulations for adolescents and adults; these contain substantially lower amounts of diphtheria toxoid and pertussis antigens. Adequate immunogenicity is achieved in adults with these lower doses for both primary and booster immunisation. Administration of paediatric doses to adults results in considerable reactogenicity and should be avoided.
- ADT refers to adsorbed diphtheria-tetanus vaccine.

The formulations listed below for children aged <8 years contain 30 IU diphtheria toxoid and 40 IU tetanus toxoid. Those for children ≥8 years contain ≥2 IU diphtheria toxoid and ≥20 IU tetanus toxoid.

Formulations for children aged <8 years

- **Infanrix hexa** (GlaxoSmithKline) contains DTPa, hepatitis B (HB), inactivated poliomyelitis vaccine (IPV), *Haemophilus influenzae* type b (Hib)
- **Infanrix-IPV** (GlaxoSmithKline) contains DTPa and IPV
- **Infanrix Penta** (GlaxoSmithKline) contains DTPa, HB and IPV.

Formulations for children aged ≥8 years and adults

- **ADT Booster** (Statens Serum Institut/CSL) contains ≥2 IU diphtheria toxoid and ≥20 IU tetanus toxoid adsorbed onto 0.5 mg aluminium hydroxide
- **Adacel** (Sanofi Pasteur) contains dTpa
- **Adacel Polio** (Sanofi Pasteur) contains dTpa and IPV
- **Boostrix** (GlaxoSmithKline) contains dTpa
- **Boostrix-IPV** (GlaxoSmithKline) contains dTpa-IPV.

Production of the previously available tetanus toxoid vaccine was discontinued in 2006. Production of the previous DT (CDT vaccine) ceased in June 2005.

Dosage and administration

- Dose: 0.5 mL administered IM.
- Can be given concurrently with any other vaccines.
- Three-dose primary course, with scheduled boosters at 4 and 12–17 years of age.

Recommendations

- Children <8 years of age should be immunised with a DTPa-containing vaccine from the list above, as part of the routine schedule.
- For those >8 years, any of the formulations listed can be given, but it is preferable to give a pertussis-containing vaccine if possible, rather than ADT booster. dTpa is certainly preferable for current or intending parents of young children, household or occupational contacts of young infants, and health workers.

Immune response and efficacy

The diphtheria and tetanus toxoids are highly immunogenic and efficacious. Almost all immunocompetent individuals, from infants to adults, develop protective diphtheria and tetanus antitoxin levels after three primary vaccine doses. Complete immunisation (five doses) induces protective levels of antitoxin lasting throughout childhood but, by middle age, about 50% of vaccine recipients have low or undetectable levels. A single dose of tetanus toxoid produces a rapid anamnestic response in such vaccinees.

High levels of transplacental diphtheria antibody in infants have been associated with lower responses to the first and second doses of diphtheria toxoid, but this effect is overcome by the third dose. The immune response to tetanus toxoid is minimally inhibited by maternal antitoxin.

The efficacy of both diphtheria and tetanus vaccines is very high, but not 100%. However, disease that occurs despite immunisation is milder and less likely to be fatal.

While no level of circulating diphtheria antitoxin confers absolute protection, there is good evidence that 0.01 IU/mL is the lowest level giving a degree of protection. However, in the absence of boosters beyond childhood, by middle age about 50% of people have antitoxin levels below this level. The herd immunity threshold to prevent outbreaks has been estimated to be 80–85% population immunity.

Booster recommendations

A single tetanus/diphtheria containing booster is recommended at 50 years of age. dTpa is preferred, as it produces immune responses to tetanus and diphtheria antigens equivalent to ADT, and also provides protection against pertussis.

Travellers to countries where health services are difficult to access should receive a booster dose if more than 10 years have elapsed since the last dose. This is because access to appropriate and safe booster immunisation may be difficult, and a tetanus booster (given full primary immunisation) should be given

for any wound >10 years after the last vaccine dose, and 5–10 years after the last dose for minor wounds which are not clean.

For those undertaking injury-prone activities in areas remote from good medical care, a booster is recommended if none has been given in the last 5 years, as this means no tetanus immunisation is required for any kind of wound, even a tetanus-prone one. Injury-prone activities include mountaineering, bike riding, rock climbing, etc.

Adverse events

Local reactions are common, and transient systemic symptoms such as fever, headache, and malaise may occur following any diphtheria and/or tetanus-containing vaccine. Both diphtheria and tetanus toxoids may contribute to reactogenicity. No serious adverse events have been associated with diphtheria toxoid.

High levels of pre-existing tetanus antitoxin are associated with (but not the sole explanation for) higher rates and severity of local reactions. Extensive limb swelling occurs most often in those with a history of multiple booster doses, and immune complex formation of tetanus toxoid with pre-existing antibody is likely to be the major mechanism. Such individuals should be evaluated and tetanus antitoxin levels assessed prior to any further booster doses being given. Most severe local reactions can be prevented by avoiding unnecessary tetanus toxoid boosters in wound management.

Acute allergic reactions occur very rarely (approximately 1 per million doses) and peripheral neuropathy, particularly brachial plexus neuropathy, may be a rare association with tetanus toxoid.

Extensive limb swelling has been observed in about 2% of children following DTPa boosters when DTPa has been used for the primary doses. This has less frequently been observed after ADT. Such swelling resolves without sequelae, and is not a contraindication to further doses. The overall reactogenicity of DTPa for primary and booster doses is significantly lower than for the whole cell pertussis-containing vaccine used in the past.

Contraindications, precautions, pregnancy and children

The only contraindication to diphtheria and tetanus toxoids is a history of previous severe adverse events associated with their use. Both are safe during pregnancy and breast-feeding.

Both are safe and should be given to the immunocompromised, though the immune response is diminished in proportion to the degree of immune impairment.

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2.4 Hepatitis A

Disease

The hepatitis A (HA) virus is a hardy, non-enveloped RNA virus shed in large quantities (up to 10^{12} viral particles per gram of stool) by infected persons, and can survive for weeks in water, marine sediment, shellfish or soil. Viral excretion peaks before the onset of symptoms and usually diminishes rapidly once symptoms develop, but infected children may shed virus for up to 6 months. Although four human genotypes and many strains of the virus are recognised, there is only one serotype, so immunity to one wild-type or vaccine strain appears to be protective against all HA viruses. Only a small proportion of infected young children develop jaundice, but 75% of infected adults develop icteric disease. The case fatality rate varies with age and is highest in older individuals (around 2% in those >40 years and up to 4% among those >60 years, compared with historic estimated mortality in hospitalised patients in Australia of 0.14% overall), and much lower among children. Older individuals also tend to have a more prolonged illness. Hepatitis A is also more often severe and complicated in those with chronic liver disease, including chronic viral hepatitis.

Occasionally a prolonged cholestatic phase occurs, and up to 10% of patients relapse clinically, biochemically, and virologically within a year. Immunity following hepatitis A infection is lifelong.

Epidemiology

Hepatitis A is a major hazard for persons from areas of low endemicity travelling to areas of medium and high endemicity (Map 5), including remote Indigenous

communities in central and northern Australia. It is consistently the second most common vaccine-preventable infection in travellers (next to influenza). However the widespread use of highly efficacious and safe vaccines in travellers has had a substantial effect. Swiss data for 1988–2004, with reporting estimated to be 80% complete, indicate a 75% reduction in imported hepatitis A notifications (Mutsch 2006). The incidence in travellers to high and intermediate regions had declined to 3–11 per 100 000 person months overall, and 6–28 per 100 000 person months in non-immune persons. These rates are 10 to 50 fold lower compared with studies in the period 1977–81, before hepatitis A vaccines became available. In Australia, as in other settings of generally low endemnicity for hepatitis A, overseas travel is the most commonly identified risk factor for sporadic cases of hepatitis A, with India, Indonesia, and Pakistan featuring prominently among source countries.

Even in high-standard hotels, non-immune travellers to intermediate and high endemicity regions are vulnerable. For budget travellers, backpackers, and trekkers the risk is up to six times greater.

The risk is even higher for those who reside in highly endemic areas for prolonged periods. For US missionaries serving in Africa (prior to HA or HB vaccine availability or use), the attack rate of hepatitis was highest during the first 2 years of service; 28% became infected with hepatitis A and 11% with hepatitis B (Lange 1990). Over the following decade, the median annual incidence rate was 5.4% for hepatitis A and 1.2% for hepatitis B.

Global patterns of HA epidemiology

Global patterns of HA epidemiology fall into three groups. In many poor areas, most children are infected in early childhood and clinical disease is uncommon. In areas of intermediate endemicity, a relatively high incidence of sporadic cases and outbreaks can occur among adolescents and young adults, and icteric HA disease may be an important public health problem. In low and particularly very low endemicity areas, infections tend to occur in specific settings and during travel. In many areas, including many parts of East and South-East Asia and southern Europe, major shifts from high to intermediate and low endemnicity have occurred in recent decades. This leaves many adolescents and young adults in such areas susceptible to infection.

The situation in Australia

Australia generally has moved from intermediate to low endemicity since the 1950s. By the mid 1990s only 1–2% of 20-year-olds were seropositive, but this increased to 50% for individuals aged >50 years and to about 60% for those >60 years (Crofts 1997). These levels of naturally acquired immunity are likely to decline further. Most immune adults do not have a history of jaundice, as most infections acquired during early childhood result in minor or no symptoms. In remote Aboriginal communities, previous data showed more than 90% of

children infected by age 5 years. One consequence of desired improvements in living conditions is a shift to intermediate endemicity, with more disease as a result of older age of acquisition of infection. During the 1990s, numerous outbreaks occurred in child day-care centres and preschools, and facilities for the intellectually disabled, as well as community-wide epidemics predominantly among men who have sex with men, and to lesser extent among injecting drug users. A large 1997 outbreak in New South Wales was associated with oysters grown in faecally contaminated waters. A marked decline in reported cases has been sustained since 2001.

Effect of immunisation program

HA vaccines have been shown to be highly effective in preventing both disease and infection, and to be extremely effective in interrupting community-wide outbreaks. In Israel and North Queensland, immunisation of toddlers alone, without a catch-up program, has resulted in near eradication of cases in the whole population within just a few years, one of the most dramatically effective results ever achieved with an immunisation program. Routine immunisation, most often of toddlers, is currently undertaken in Aboriginal and Torres Strait Islander children in Queensland, Northern Territory, South Australia, and Western Australia; and in Israel, Puglia (Italy), Catalonia (Spain, adolescent immunisation), the United States, and Argentina.

Hepatitis A immunisation

Monovalent vaccines

Three different monovalent hepatitis A vaccines are available in Australia; in addition, combined HA-HB and HA/typhoid (Vi) vaccines are available. These vaccines include different strains of virus grown on human diploid (MRC-5) cells, inactivated by formaldehyde, and adsorbed onto aluminium hydroxide adjuvant.

- **Havrix** (GlaxoSmithKline) contains strain HM175 of HA virus. This strain is derived from virus isolated at Fairfield Hospital in Melbourne from a man hospitalised with hepatitis A together with his whole family following ingestion of shellfish from Port Phillip Bay. This vaccine is presented as Havrix 1440 (1 mL), containing 1440 ELISA units of viral antigens, and Havrix Junior (0.5 mL), containing 720 ELISA units of HA antigens.
- **Vaqta** (manufactured by Merck & Co Inc, distributed by CSL Biotherapies) is based on the CR326F strain from Costa Rica. Again the adult formulation is presented as a 1 mL dose containing twice the antigen content (50 units) of the paediatric/adolescent formulation (25 units) presented as a 0.5 mL dose.
- **Avaxim** (Aventis Pasteur) contains the GBM strain; each 0.5 mL dose contains 160 ELISA units of viral antigens. Identical adult and paediatric doses

of this vaccine are recommended in Australia; in a number of other countries half this dose is used for children under 16 years of age.

Due to the different assays used and the lack of an accepted standard, each manufacturer uses different units, not directly comparable, to express the HA antigen content of their vaccine. While Vaqta is formulated without a preservative, Havrix and Avaxim (and the respective combination vaccines Twinrix and Vivaxim) contain 2-phenoxyethanol. All the vaccines other than Vaqta contain trace amounts of neomycin, and all contain trace amounts of residual formaldehyde. Differences in the content of non-virion proteins exist between the vaccines but have not been found to be clinically relevant. The 'equivalent' vaccines of the different manufacturers are interchangeable: a course begun with one vaccine can be completed with a different vaccine.

An additional HA vaccine – **Epaxal**, licensed by Berna Biotech – is available in Europe, Canada, New Zealand, and other countries. It includes a liposomal adjuvant composed of reconstituted H1N1 influenza virosomes. A live attenuated vaccine is licensed and has been widely used in China.

Dosage and administration

All HA-containing vaccines are given by IM injection; the recommended doses and schedules are listed in Table 2.4.1.

All HA-containing vaccines, like all alum-adjuvanted vaccines, should be stored meticulously at 2–8°C and must not be frozen.

Delayed vaccine doses

A common issue with HA immunisation in travellers is delay in receipt of the second dose. A number of studies have evaluated administration of the second dose up to 6 years after the first; all have shown an excellent response in all subjects after the second dose, comparable to that observed with a second dose given 6–12 months after the first.

Table 2.4.1 Monovalent HA vaccines

Vaccine	Age (years)	Dose	Volume (mL)	Schedule
Avaxim	≥2	160 EIA U	0.5	0, 6–12 months
Havrix Junior	2–15	720 ElA U	0.5	0, 6–12 months
Havrix 1440	≥16	1440 ElA U	1.0	0, 6–12 months
Vaqta Ped/Adol	1–17	25 U	0.5	0, 6–18 months
Vaqta	≥18	50 U	1.0	0, 6–18 months

Thus any vaccine doses given do not need to be repeated, no matter how long has elapsed; missing doses should simply be given to bring the schedule up to date.

These studies also suggest that following a single dose of Havrix, protection can be regarded as reliably persisting for at least 12 months, and in most subjects for a few years. Thus we believe a good deal more flexibility exists in the dosage regimen for HA than the recommended schedules suggest.

Immune response

HA vaccines are highly immunogenic, with >95% of children and adults, and in many studies close to 100% of subjects, developing protective antibody levels after immunisation. The absolute lower limit of antibody needed to prevent HA infection has not been determined. Levels of 10–20 mIU/mL achieved 1–2 months after immunoglobulin are known to be protective.

Because the response rate to HA vaccines is so high, and the antibody titres achieved are not infrequently below the limits of detection of routine commercial assays, post-immunisation antibody testing is not recommended. A negative result on an antibody test following immunisation does not mean the patient is not protected.

It should be noted that antiHA IgM – the assay usually performed for the diagnosis of hepatitis A infection – may be detectable by standard assays if measured within the first few weeks following immunisation.

Efficacy

Efficacy studies have been conducted for three HA vaccines. Havrix was evaluated in a large field trial involving 40 000 children in Thailand (after two 360 EIA U doses, less than currently used) (Innis 1994), and Vaqta in 1037 children in a US community with high rates of HA (Werzberger 1992). Both showed impressively and similarly high efficacy, when judged by the same criteria. Rare vaccine failures have been described with both vaccines, but effectiveness is >99%. The Thai Havrix study showed, importantly, that the vaccine had about 95% efficacy against infection, as well as against disease – hence its power as a public health tool. Use of both vaccines to control community HA outbreaks in various settings has been highly effective when good coverage has been achieved. In a Nicaraguan trial of the virosome vaccine in children aged 1.5 to 6 years, the efficacy was 100% (Perez 2003).

Efficacy in a post-exposure setting has also been evaluated. In Italy, household contacts of hospitalised cases were given Havrix alone or no treatment within 8 days of symptom onset in the index case. The efficacy of this strategy was found to be 79%. Only two cases occurred in vaccine recipients and both were asymptomatic with normal ALT. In contrast 10 out of 12 cases in the control group were symptomatic with raised ALT, suggesting that the clinical course of

infection not prevented by immunisation was ameliorated (Sagliocca 1999). A large trial of Vaqta compared with immunoglobulin for post-exposure prevention of hepatitis A in contacts of cases in Kazakhstan showed a similar high efficacy for both interventions (Victor 2007). On the basis of these results CDC now recommends vaccine rather than immunoglobulin for healthy contacts aged 1–40 years of cases of hepatitis A.

Boosters

At present there is no demonstrated need, and no recommendation anywhere, for booster doses of HA vaccine.

The longest follow-up data are available for Havrix, which was the first HA vaccine to be licensed. Long-term follow-up of immunised cohorts of adults and children have demonstrated an initial, more rapid antibody decay in the first year and then very slow decline, with GMT after 10 years still being several hundred mIU/mL. Modelling antibody kinetics predicts that protective levels of antibody will persist for between 25 and 35 years following immunisation, and it is possible that immune memory will result (as for HB) in persistence of protection for longer than persistence of antibody. Thus any need for HA boosting remains to be established, and is not likely to be needed for many years, if ever.

Adverse events

- **Local**: Injection site pain, redness, induration and swelling are reported in about 50% of adults and about 20% of children. Most are mild and disappear within 1–2 days. They are most likely related to the alum adjuvant, and are less frequent with Avaxim, probably related to the lower volume of injection and adjuvant content.
- **General**: Headache is reported in about 15% of adults (less commonly in children), and systemic reactions including malaise, fatigue, fever, and nausea in approximately 5% of adults. These are commonly mild and brief in duration.
- **Serious adverse events**: Haematological, immunological, and neurological events (for example Guillain-Barré syndrome, brachial plexus neuropathy) have not occurred more commonly in vaccine recipients than would be expected among the unimmunised population. No serious adverse events have been demonstrated to be associated with hepatitis A vaccines, including in immunocompromised persons.

Contraindications and precautions

Contraindications are restricted to previous anaphylaxis to a vaccine component or a previous dose of a HA vaccine.

- **Immunocompromised persons**: The vaccine is safe in immunocompromised persons (but may be less immunogenic, in proportion to their degree of immunoparesis), and there is no increase in adverse events in those already immune to HA.
- **Pregnancy**: The safety of the vaccine in pregnancy has not been specifically assessed, but as the vaccine is produced using inactivated HA, no risk to the developing fetus or the mother is expected. The NHMRC does not consider pregnancy a contraindication to HA immunisation.
- **Children**: The vaccine is safe and immunogenic in children. The lower approved age limit for the monovalent vaccines is 1 year for Vaqta and 2 years for Avaxim and Havrix, but the latter is inconsistent with the lower approved age limit for Twinrix being 1 year (see discussion of combined hepatitis A and B immunisation below). HA vaccines have been extensively evaluated in infants and in toddlers, in whom they are immunogenic and well tolerated. The antibody titre is reduced, but seroconversion and immunological priming are unaffected when Havrix is given to infants of HA seropositive mothers. This interference from maternally derived antibody can be overcome by an additional vaccine dose in the second year of life. We are completely comfortable with use of vaccine, particularly Havrix for which most data are available, from 12 months of age. In most areas where routine immunisation of toddlers is undertaken, including in a number of Australian states and in the United States, the first hepatitis A vaccine dose is recommended at 12 months of age.

Recommendations

HA immunisation is recommended for all travellers to areas of moderate to high endemicity, which essentially means to all developing countries, irrespective of type or duration of travel or activities planned, and includes those who live and work in rural and remote Australian Indigenous communities.

Other NHMRC indications for HA immunisation are documented in *The Australian Immunisation Handbook*.

Pre-immunisation screening

The NHMRC recommends pre-immunisation screening of those with increased probability of existing immunity to HA:

- those born before 1950
- those who spent their early childhood in high incidence areas, including in Indigenous communities
- those with past unexplained jaundice (such an episode should not be assumed to be HA).

Pre-immunisation screening for total (or IgG) antiHAV has been shown to be cost-effective when the prior probability of immunity is about 50% or higher. However, performing a test and acting on the result often involves more time, visits and complexity, and may not always be practical, so practitioners should err on the side of immunising rather than not immunising to ensure that all travellers to areas of poor or uncertain hygiene are protected against HA.

When testing to assess prior immunity, it is important that total or IgG antibodies be requested. The IgM test performed to diagnose current or recent HA infection remains positive generally only for 6 months following infection, and thus is not appropriate to define prior immunity.

Last-minute travellers

NHMRC (2008) recommends that there is no place for the routine use of normal human immunoglobulin (IG) for HA prevention in travellers and that concurrent IG should only be given to those at very high risk of HA, such as aid workers to be deployed within 2 weeks to emergency refugee camps or living in very inadequate circumstances. CDC (2012) recommends that for optimal protection, older adults, immunocompromised persons and persons with chronic liver disease or other chronic medical conditions planning to travel within 2 weeks should receive IG along with the initial dose of vaccine. This results in a similar seroconversion rate, but 50% reduction in antibody levels, compared with vaccine alone. We concur with WHO (2011) that the use of IG is virtually obsolete for travellers, and that **vaccine alone can be used for travellers right up to the day of departure**, as there is strong evidence that vaccine works right up to and even after exposure:

- Post-exposure immunisation is efficacious. Immunisation given before exposure, even very shortly before, can be assumed to be at least as if not more effective.
- The average incubation period of hepatitis A is 28 days. Yet among vaccinated subjects in several outbreak settings, there has been a rapid drop-off in cases of HA, with no further cases more than 3 days to 3 weeks (and generally at the shorter end) after the first vaccine dose.
- Seroconversion is rapid: 88–96% of adults are seropositive 2 weeks after a dose of Havrix, and 98% are seropositive (in a different assay) 2 weeks after a dose of Vaqta, well within the usual incubation period of HA. The low levels of antibody achieved after administration of IG are known to offer substantial pre- and post-exposure protection.
- The incidence of HA has continued to decline, including in travellers, in countries with good surveillance systems where pre-exposure IG has not been used for several years, for example Switzerland and France.

- There are few if any reports of early breakthrough infections in travellers given the vaccine <2 weeks pre-departure.
- Further, as noted below, there are good reasons to restrict prophylactic use of IG as much as practicable: it is expensive; it is in short supply; it has important therapeutic uses; although it has no proven risks, there are theoretical issues associated with a blood product including transmissible spongiform encephalopathies; and IG provides only short-lived, incomplete protection. It should be replaced in almost every circumstance for prevention by active, highly efficacious active immunisation providing long-term protection.

Immunocompromised travellers

The only indication we see for IG in the prevention of HA in travellers is for those who are substantially immunocompromised, so that the immunogenicity of most vaccines is reduced. If such travellers are shown to be susceptible to HA, we believe the combination of HA vaccine together with IG (the latter best administered shortly before departure) can be expected to provide the most effective protection.

For short-term protection (up to 2 months), a 2 mL dose of Normal Immunoglobulin-VF (human) (NHIG) should be administered intramuscularly. For longer term protection (3–5 months), a 5 mL dose should be given.

Children

We favour use of HA immunisation for young travellers, and there is growing support for this view. The following points have informed this view:

- While most early childhood HA infections are asymptomatic, clinical disease including fulminant hepatitis can occur.
- Children are common sources of infection for susceptible older contacts.
- Illness becomes more likely with increasing age.
- Vaccine is safe and provides a high level of protection probably for at least a few decades – well into adult life. It may as well be given at the earliest opportunity to provide greatest benefit.
- Children who travel abroad are likely to travel repeatedly in future years.
- Sustained and substantial improvements in hygiene and sanitation with reduced likelihood of exposure to HA are not foreseeable in the near future in many parts of the world.
- HA vaccine is used routinely in childhood in a number of places. Such use has been shown to be safe and highly effective and is likely to expand.

While it is arguable that HA immunisation could be omitted for children <5 years undertaking short-term travel (<2 weeks at risk), particularly once-off, we feel the ongoing benefits of immunisation warrant use of the vaccine for children

aged 12 months and older. We particularly recommend HA immunisation for children aged 1–5 years for longer term or repeated travel, and for children >5 years for short-term travel. The number of injections involved can often be minimised by use of an appropriate combination vaccine, usually the HA-typhoid combination since hepatitis B is included in routine infant immunisation.

Hepatitis A vaccine is indicated for children 1–5 years of age, particularly those who undertake repeated or prolonged travel.

Combined hepatitis A and B immunisation

Vaccine

HA-HB – Twinrix (GlaxoSmithKline) is a non-infectious combination vaccine containing inactivated hepatitis A virus and genetically engineered hepatitis B surface antigen (HBsAg). There are two formulations: Twinrix, a 1 mL dose containing 720 ELISA units of inactivated HAV and 20 µg of recombinant HBsAg protein (720/20 formulation); and Twinrix Junior, a 0.5 mL dose containing 360 ELISA units of HA and 10 µg HBsAg (360/10 formulation). The components of this vaccine are identical to those in the respective monovalent vaccines from the same manufacturer.

Dosage and administration

- Dose (adults): 1 mL; primary course consists of three doses of vaccine given at 0, 1 and 6 months (the three-dose schedule is necessary for the hepatitis B component). The rapid schedule of 0, 7, 21 days and 12 months can be very useful to provide good protection against both hepatitis A and B for travellers, but like all compressed HB immunisation schedules, requires a booster dose at 12 months.
- For children and adolescents who have not previously been immunised against hepatitis B, the two-dose schedule of Twinrix using the 720/20 formulation provides an alternative involving a total of only two rather than

Table 2.4.2 Combination HA-HB vaccines

Vaccine	Age (years)	Dose	Volume (mL)	Schedule
Twinrix Junior (360/10)	1–15	360 EIA U HA, 10 µg HBsAg	0.5	0, 1, 6 months
Twinrix (720/20)	≥16	720 EIA U HA, 20 µg HBsAg	1.0	0, 1, 6 months
Twinrix (720/20)*	1–15	720 EIA U HA, 20 µg HBsAg	1.0	0, 6–12 months
Twinrix (720/20)**	≥16	720 EIA U HA, 20 µg HBsAg	1.0	0, 7, 21 days, 12 months

* A three-dose HB or HA-HB schedule should be used in preference to the simpler two-dose Twinrix schedule for children if early protection is required for hepatitis B, as 80% or better seroprotection is achieved following a second dose of HB vaccine in a three-dose schedule.
** This rapid schedule should be used only if early protection is required against hepatitis B (e.g. prior to overseas travel).

three vaccine doses; however this is not suitable if prompt protection against hepatitis B is needed.

- Twinrix Adult should be injected intramuscularly in the deltoid region. Exceptionally, it may be administered subcutaneously in patients with thrombocytopenia or bleeding disorders.
- Twinrix Adult is a ready-to-use suspension. It must be shaken well before use. After shaking, the vaccine is a slightly opaque white suspension. Discard if the contents of the vial appear otherwise.

Immune response and efficacy

Twinrix Adult induces the production of specific antiHAV and antiHBs antibodies, which confer immunity against HAV and HBV infection.

The response to the HA component of this combined vaccine is identical to that to Havrix. However, for HB, while the final immune responses after combined and monovalent vaccines are similar, there is evidence of a somewhat brisker HB antibody response, with 10–15% higher seroprotection and somewhat higher antibody titres after the second dose with the combined vaccine. Further, a higher seroprotection rate is achieved in older subjects with the combined HA-HB vaccine than with the respective monovalent vaccine, Engerix B (88.2% vs 73% respectively in those >60 years in a large German study). Thus the combined vaccine has advantages from a HB point of view both in those who may not complete the course and in older subjects.

The two-dose HA-HB schedule approved in children aged 1–15 years provides a welcome simpler schedule but **should not be used if HB protection is urgently needed**, such as for travellers or known contacts of infected person/s, as only about 40% of subjects are seroprotected after the first dose of a two-dose schedule, whereas ≥90% of subjects are seroprotected after the second of three doses.

As for monovalent HB vaccine, a rapid schedule of 0, 7, 21 days and 12 months is very helpful for travellers who so often present with limited time available before departure. The 12-month dose provides an increment in seroprotection rate (from 95% to 100% in a large German study (Rendi-Wagner 2001)) and a large increase in antibody titre.

A useful practical point is that HA and HB immunisation commenced with the monovalent vaccines can be completed at any point in the schedule with HA-HB vaccine with comparable seroconversion rates.

Boosters

As the combined HA-HB vaccine performs as well as the respective monovalent vaccines, the same booster recommendations apply to the combined vaccine as to the monovalent ones.

Adverse reactions

In controlled trials, most adverse events were considered by the subjects to be mild and transient. No serious adverse events considered related to vaccination were reported. In a comparative trial it was found that the frequency of adverse events following administration of Twinrix Adult was not different from that with either the monovalent hepatitis A or hepatitis B vaccines.

Recommendations

HA-HB vaccine is recommended for those at risk of both infections, including:

- expatriates and long-term visitors to developing countries
- medical, dental and nursing students
- Indigenous populations and certain communities in industrialised countries (e.g. Aboriginal Australians and Eskimos)
- men who have sex with men
- sex workers
- injecting drug users
- patients with chronic liver disease, particularly hepatitis C
- residents and staff of institutions for intellectually disabled persons
- people with haemophilia
- military personnel.

The availability of the combined vaccine means that complete courses of immunisation against hepatitis A and B can be administered with a total of two or three, rather than five injections, simplifying vaccine administration, storage, handling and record keeping, and lessening overall side-effects.

It is appropriate for health workers to ask themselves whether combined hepatitis A and B vaccine is indicated whenever the issue of immunisation against either hepatitis A or B arises.

The availability of combined vaccine means that whenever hepatitis A or B vaccines are indicated, practitioners should consider whether the other is also indicated.

Use of combined hepatitis A and B vaccine in children

- **Vaccine**: Twinrix Junior is identical to Twinrix Adult except that the dose (720 EIA U inactivated HAV and 20 µg of recombinant HBsAg protein) and volume (0.5 mL) are half those of the adult presentation.
- **Schedule**: Twinrix Junior is recommended in the same schedule as for adults (0, 1 and 6 months) for children and adolescents aged 1–15 years. (Note:

The monovalent Havrix and Avaxim vaccines are not formally approved in Australia for use in children <2 years of age, although this is inconsistent and the monovalent vaccines, particularly Havrix, are widely used in toddlers in various national immunisation programs, including in Australia.)

- **Immune response**: Studies in children show immunogenicity of the combined preparation equivalent to that of the separate hepatitis A and B vaccines. A slightly more rapid antibody response is seen in children than in adults. In clinical trials in children, seroconversion rates to both components of 99–100% have been observed.
- **Use**: A good argument can be made for universal hepatitis A immunisation and, therefore, for widespread use of the combined vaccine in children and adolescents who have not already been immunised against HB. Universal immunisation is the only measure likely to achieve control and potential eradication of hepatitis A. However, a combined vaccine including both hepatitis A and B suitable for use in infants is not yet available, and infancy, preferably commencing at birth, is the optimal time for HB immunisation. A variety of combination paediatric vaccines including HB are already available. In the future, hepatitis A may also be combined with other paediatric immunogens, but this does not appear to be on the horizon anytime soon.

Unfortunately, the cost of Twinrix is currently 10–30% higher than the total cost of the separate vaccines.

Combined hepatitis A and typhoid immunisation

Vaccine

HA/Vi-Typhoid: Vivaxim (Sanofi Pasteur) combines the separate vaccines (the same as the respective monovalent vaccines from the same manufacturer) supplied in a unique dual-chamber syringe, mixed just prior to administration to constitute a 1 mL dose. This dual chamber syringe is rather cumbersome and the combined HA/Vi vaccine should be used promptly after mixing. The vaccine contains 160 ELISA units of HA antigens and 25 μg typhoid Vi capsular polysaccharide (CPS).

Dosage and administration

Dose: a single 1 mL given intramuscularly.

Duration of immunity and booster recommendations

A dose of monovalent adult formulation HA vaccine at 6–36 months will provide long-term immunity. Duration of protection against typhoid is about 3 years. Repeat typhoid immunisation could be administered together with a second (booster) dose of HA vaccine using the combined vaccine after 3 years,

if ongoing typhoid protection is indicated. (A true booster effect is not observed with plain polysaccharide vaccines.)

Recommendation

The NHMRC states that this vaccine can be recommended for all those ≥16 years who intend travelling to developing countries (presuming that immunisation against both HA and typhoid are indicated and that HB immunisation is not required). It can be used either as the primary or the booster dose of HA vaccine, and the first or a repeat dose of typhoid vaccine. The main utility of the HA/Vi vaccine is for the growing proportion of the travelling population, particularly adolescents and young adults, already immune to HB.

The separate HA and typhoid vaccines from the same manufacturer are licensed for use from the age of 2 years, while Vivaxim is licensed only for those 16 years and older. However, we are not aware of any particular age-related safety or efficacy issues with either the combined or separate vaccines, and therefore a number of the authors have been prescribing Vivaxim for children from 2 years of age (off-label) for years.

Choice of hepatitis A vaccine

We do not have a strong preference in choice of monovalent HA vaccine, except that, cost factors aside, we would generally favour the vaccine for which the largest body of experience, including efficacy data, is available (Havrix).

All available evidence suggests that a course of immunisation commenced with one HA vaccine can be completed with another, including combination vaccines.

When immunisation against HA, HB and typhoid is indicated, we favour HA-HB plus separate Vi rather than HA/Vi plus separate HB, for the following reasons:

- the total number of injections is four (except if the rapid schedule is used) rather than five
- the brisker HB response seen after two doses and better HB immunogenicity in older persons with the HA-HB vaccine.

Immunoglobulin

Normal human immunoglobulin (NHIG, or simply IG) (CSL Bioplasma) is prepared from large pools of plasma collected from Australian Red Cross blood donors.

IG contains 16% immunoglobulin, mostly IgG, and includes antibodies commonly present in adult blood, which is why it contains protective levels of antibodies against HA and measles. IG is not associated with any known risk of disease transmission, although this may not be true of IG produced in

developing countries. Used prior to or within 2 weeks of exposure, IG is at least 85% efficacious in preventing HA, and the severity of illness not prevented is generally reduced. However, fulminant HA has been described following IG administration.

IG is expensive (to the taxpayer rather than the patient), in short supply, has multiple therapeutic uses, is a blood product, provides incomplete and short-lived protection, and may involve a large and painful injection.

NHMRC (2008) recommends 'there is no place for the routine use of NHIG to prevent hepatitis A in travellers'. The only indications for IG for travellers are:

- moderate or severe immune compromise, when a protective response to the vaccine is unlikely; though we would still recommend vaccine in addition to IG unless only brief protection is required
- severe reaction to a previous vaccine dose or to a vaccine component.

NHIG continues to be recommended (e.g. NHMRC 2008) for the prevention of hepatitis A in contacts of cases. Though this topic is largely outside our present scope, for similar reasons to those for use of HA vaccine right up to and indeed after commencement of travel, and evidence from interruption of outbreaks and two intervention trials, we favour the use of HA vaccine in the public health management of contacts of cases, as CDC now recommends for those aged between 1 and 40 years.

Note: Passively acquired antibody may interfere with replication of live vaccine viruses such as measles, mumps, rubella and varicella, and the immune response to vaccines containing them. Use of these vaccines should be delayed (or the dose repeated) at least 3 months after the administration of intramuscular IG, and at least 9 months after administration of NHIG (intravenous). If these vaccines are given first, at least 2 weeks should elapse before IG is given.

Hepatitis A vaccines can be given alone right up to or after the day of departure.

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2.5 Hepatitis B

Hepatitis B (HB) is one of the most important viral pathogens of humans. HB is the most contagious of the common blood-borne viruses. Hepatitis B surface antigen (HBsAg) has been identified in virtually every body fluid of infected persons, and as well as being blood-borne is infectious in semen, vaginal fluid and saliva at least. The virus can be present in very large quantities, particularly in blood and serum. It is stable in the environment – virus air-dried at room temperature is infectious for at least one week.

The key determinant of the outcome of infection is the age at which it occurs. Acute icteric disease is uncommon in young children, but affects 30–50% of infected adults. On the other hand, chronic infection, causing the bulk of the morbidity and mortality associated with HB, follows about 80–90% of infant infections, 30–60% of infections between 1 and 4 years of age, and less than 5%

of adult infections. Chronic infection is rare in those who develop acute icteric disease.

Epidemiology

Approximately 30% of the world's population – about 2 billion people – have been infected at some time. An estimated 20 million new infections occur worldwide annually, about 350 million are chronically infected, and about 620 000 of these die each year due to chronic liver disease – cirrhosis and/or primary liver cancer. About 45% of the world's population live in areas where the prevalence of chronic infection is high (≥8%), and a further 43% live in areas of moderate prevalence, where 2–7% of the population is chronically infected (Map 6). Areas of high prevalence include most of East, South-East and Central Asia (approximately 75% of the world's HB carriers live in Asia), Sub-Saharan Africa, Pacific Island countries, and parts of the Middle East, South America and eastern Europe. Indigenous populations in a number of areas including Australia have a high prevalence of HB infection. Universal infant immunisation programs are making a big difference – for example, in the WHO Western Pacific Region, HBsAg prevalence among 5-year-old children is estimated to have declined from 9.2% in the pre-immunisation era to about 1.7% by 2007. However, most of the large number of those chronically infected will remain infected for life, and mortality due to hepatitis B in the Western Pacific Region remains higher than deaths from tuberculosis.

For overseas workers (missionaries and health-care personnel) in developing countries, studies in the 1980s and early 1990s showed the monthly incidence of hepatitis B infection is estimated to be 80 (Africa, Latin America) to 240 (Asia) per 100 000, with respective rates of symptomatic infection being 20 to 60 per 100 000 per month. Other data suggest rates of infection up to 420 per 100 000 expatriates per month. For short-term travellers the rates were several-fold lower. This makes HB generally the third most common vaccine-preventable infection of travellers. Because the mortality of HB is higher than that of HA, the mortality of HB is estimated to be comparable to that of HA for travel to Latin America or Africa (1.6 versus 0.3–2 per 100 000 per month in non-immune travellers) and higher following travel to Asia (4.8 per 100 000 per month). Australian adult travellers frequently engage in activities that place them at risk of exposure to blood-borne agents (Table 2.5.1). In annual national surveys undertaken between 2000 and 2004, between 32% and 51% of adult travellers reported participating in at least one activity involving potential risk of exposure to HB during their most recent overseas trip in the previous 2 years.

Vaccines

Two recombinant hepatitis B vaccines available in Australia contain HBsAg particles expressed from recombinant DNA in yeast cells. Synthesised HBsAg protein assembles into immunogenic particles which differ from the natural

Table 2.5.1 Reported participation in activities associated with potential risk of exposure to blood-borne agents by Australian adult travellers

Activities overseas most commonly associated with potential risk of exposure to blood-borne agents	Proportion of respondents undertaking behaviour during their last overseas trip, range 2000–04 (%)
Water sports other than swimming	10–22
Motorcycle or off-road vehicle use	11–23
Consulted doctor or nurse abroad	10–16
New sexual contacts (not with regular partner)	5–8*
Played contact sport	4–8
Any kind of injury	5–8
Received an injection	2–3
New sexual contact without condom	1–3
Dental care	2–3
Contact with other's blood or gave first aid	0–3
Body piercing or tattoo	1–2
Shared razor or toothbrush with newly met person	1*
Received a blood transfusion	0.25

N = 503 (2000), 507 (2001), 500 (2002), 503 (2003), 309 (2004)
* Data for 2003–04. Source for 2003 data: Zwar 2003

particles only in that synthetic HBsAg is not glycosylated. The monovalent vaccines are:

- Engerix-B (GlaxoSmithKline)
- H-B-Vax II (Merck/CSL Biotherapies)

The same HB vaccines are included in a variety of combination vaccines for paediatric use.

Vaccines containing the Merck vaccine:

- HB-Hib(PRP-OMP) – Comvax

Vaccines containing the GSK vaccine:

- DTPa-HB-IPV – Infanrix Penta
- DTPa-HB-IPV/Hib(PRP-T) – Infanrix Hexa

The GSK vaccine is also available combined with HA in two different formulations (discussed in detail in chapter 2.4, Hepatitis A):

- HA-HB – Twinrix (720/20) and Twinrix Junior (360/10)

The considerable heat stability of HB vaccine can be useful in practice, but it is highly susceptible to freezing damage (the vaccine freezes at around –0.5°C). HB vaccine can be stored at room (including tropical) temperatures for at least a month with minimal loss of potency.

Numerous studies have shown that HB vaccines from different manufacturers are interchangeable during a course.

All HB-containing vaccines available in Australia are now free of thiomersal.

Dosage and administration

There is a good deal of flexibility in HB vaccine schedules, which can be used to advantage to optimise protection for travellers – particularly when using rapid schedules. There is some specificity of particular approved schedules for particular vaccines. The NHMRC recommended schedules for monovalent HB vaccines are outlined in Table 2.5.2; for schedules for HA-HB vaccine, see chapter 2.4; for combination paediatric vaccines, please refer to the current edition of *The Australian Immunisation Handbook*.

All HB-containing vaccines are given by IM injection (anterolateral thigh in infants, deltoid in older children and adults), except in the context of a bleeding tendency or thrombocytopenia with platelet count $<50 \times 10^9$/L, when the subcutaneous route should be used if correction is not feasible.

Immune response and efficacy

Seroconversion

Following a three-dose HB vaccine course, seroprotective levels of antibody are achieved in well over 95% of healthy infants, children and adolescents, over 90% of adults under 40 years, and a decreasing proportion of older individuals (for seroprotection level, see 'Efficacy of HB vaccine'). By age 60 years, the seroprotection rate may decline to as low as 65–75%.

Among healthy adults <40 years, seroprotection rates are 30–55% after the first dose, and 75% after the second dose.

The rapid (0, 1, 2 months) and accelerated (0, 7, 21 days) schedules for Engerix-B should be followed by a fourth dose at about 12 months, as should the 0, 7, 21 days schedule for Twinrix. This has the effect of increasing the seroprotection rate from a little over 90% to close to 100%, and of dramatically increasing the antiHBs titre.

A longer interval between the second and third doses is associated with a higher antibody level, but this must be balanced against later onset of optimal protection.

Table 2.5.2 Monovalent HB vaccine schedules, NHMRC (2008)

Vaccine	Age (years)	Dose HBsAg**	Volume (mL)	Schedule
Common to both vaccines				
Engerix-B and H-B-Vax II (adult formulations)	≥20	20 µg Engerix-B; 10 µg H-B-Vax II	1 mL	0, 1–2 months, 2–5 months between 2nd and 3rd doses (e.g. 0, 1, 6 months)
Engerix-B and H-B-Vax II (paediatric formulations)	<20	10 µg Engerix-B; 5 µg H-B-Vax II	0.5 mL	0, 1 month, 2–5 months between 2nd and 3rd doses (e.g. 0, 1, 6 months)
Vaccine-specific				
Engerix-B (adult)	≥20	20 µg	1 mL	0, 1, 2, 12 months (rapid schedule) or 0, 7, 21 days; 12 months (accelerated schedule)
Engerix-B (paediatric)	<20	10 µg	0.5 mL	0, 1, 2, 12 months (rapid schedule)
Engerix-B (adult formulation)	11–15	20 µg	1 mL	0, 6 months (2-dose schedule)
H-B-Vax II (adult formulation)	11–15	10 µg	1 mL	0, 4–6 months (2-dose schedule)
H-B-Vax II * (dialysis formulation)	≥20, immune compromised	40 µg	1 mL	0, 1, 6 months

* For immunocompromised adults either the dialysis formulation or a double dose of either standard adult vaccine is recommended.
** Note that the dose of HBsAg in vaccines from different manufacturers is not strictly comparable.

Decline of antibodies

The maximum level of antiHBs after completion of the primary course is predictive of the persistence of antibody, but the rate of decline is independent of the initial antibody titre.

Antibody titres decline fairly rapidly in the first year following completion of the vaccine course, and more gradually thereafter.

Among infants and children who respond to a primary three-dose series, 15–50% lose detectable antibody over the course of 5–15 years. In adult vaccinees, antibody levels fall below 10 mIU/mL in 7–50% after 5 years in different studies, and in 30–60% within 9–11 years.

Nevertheless, more than 95% of subjects of all ages who responded to the primary series and lose detectable antibody after 5–13 years will respond with a

brisk (anamnestic) booster response to a subsequent booster dose, indicating preserved immunological memory. It is such an anamnestic immune response after HB virus exposure that is thought to be the mechanism for long-term persistence of protection after immunisation.

Efficacy of HB vaccine

Early efficacy studies of HB vaccine demonstrated, and subsequent studies have confirmed, virtually complete protection against disease and acute and chronic infection among those who develop an antiHBs titre of ≥10 mIU/mL following immunisation, and lesser protection among those who seroconvert (develop detectable antibody) but do not achieve this 'seroprotective' level, which is considered to be the marker of an adequate protective immune response to immunisation.

Despite the decline in antibody over time, frequently to undetectable levels, among those who initially achieved a seroprotective level of antibody, clinical disease has not been observed in follow-up of immunocompetent vaccine responders, and only rare breakthrough chronic infections have been documented in infants born to an infected mother. No chronic breakthrough infections have been observed in adult responders. Immunocompromised persons, however, are protected only while antiHBs levels remain ≥10 mIU/mL.

Differences between vaccines: Do dose and antibody level matter?

There is no international standard of HB vaccine potency expressed in amount of HBsAg protein, and the relative immunogenicity or efficacy of different vaccines is not equivalent microgram for microgram of antigen content. Paediatric HB vaccine doses worldwide vary between 1.5 and 10 μg, and the recommended dose for each vaccine should be used. That said, there clearly exists a degree of broad correlation between dose and immunogenicity among vaccines, and the differences in potency per microgram between different vaccines do not vary by anything close to an order of magnitude.

Higher dose vaccines are associated with a more rapid antibody response, especially after the second dose. This provides earlier protection and is an advantage if the third dose is delayed or missed. In addition, higher dose vaccines achieve a higher seroprotection rate in the presence of factors that increase the likelihood of a poor vaccine response. These include age >40 years, obesity, smoking, male sex and chronic disease. Certain HLA types are associated with HB vaccine non-response.

It is noteworthy that the best seroprotection rates in those less likely to respond well to HB vaccine have been observed with Twinrix. In a large non-randomised but unselected study in German travel clinics, including more than 400 persons aged over 60 years, the seroprotection rate in this age group following three doses of Twinrix was 88.2%, following was Engerix-B with 73%, and following was the Merck HB vaccine with 56.3% (Rendi-Wagner 2001). While the

difference between vaccines was most marked at older ages, a similar trend was observed in all age groups.

Booster doses

Currently most major authorities, including NHMRC, WHO, CDC and the Viral Hepatitis Prevention Board do not recommend routine booster doses in immunocompetent persons of any age or occupation. Whether and when booster doses might be needed can only be addressed by long-term follow-up studies.

Occupational risk

All healthcare workers and others at occupational risk, particularly those going to work in high prevalence populations, should be optimally protected against HB and have their immune status documented. This may involve one or more additional vaccine doses (see below: Testing for immunity after immunisation, and Management of non-responders).

Immunocompromised travellers

In immunocompromised persons, including those with HIV infection or renal failure, antiHBs levels should be measured every 12 months and vaccine booster doses given as needed to maintain antibody levels above 10 mIU/mL.

Adverse events

- Systemic symptoms such as nausea, malaise, and dizziness are uncommon. Fever, usually low grade, occurs in 2–3%.
- Soreness at the injection site occurs in 3–29% of immunised persons, and is generally mild, lasting less than 24 hours.
- Anaphylaxis and transient alopecia are rare. Adrenaline should always be available for immediate use when any vaccine is administered.
- Serious adverse events, such as Guillain-Barré syndrome, multiple sclerosis, other demyelinating disorders, diabetes mellitus, rheumatoid arthritis, and other autoimmune diseases are not associated with HB vaccine.
- There are no benefits or particular adverse events associated with administration of vaccine to a person either chronically infected or already immune to HB.

Contraindications and precautions

The vaccine is safe and indicated at all ages from birth, and with any cause or degree of immunoparesis.

Contraindications are limited to previous anaphylactic reaction following a HB vaccine dose, or anaphylactic sensitivity to any vaccine component. Anaphylactic allergy to baker's yeast is a theoretical contraindication, but there is no convincing evidence of problems with the vaccine related to yeast allergy.

Neither **pregnancy** nor lactation constitute contraindications to HB immunisation, though, all other things being equal, as with other immunisations, we would favour the second and third trimesters over the first.

Interactions

Hepatitis B vaccine can be given at any time in relation to any other immunising agent. Co-administration with HBIG is indicated for infants born to HB-infected mothers, or for exposures in susceptible persons. As noted, co-administration with HA in the form of the combined HA-HB (Twinrix) vaccine appears to provide some augmentation of the immunogenicity of the HB component.

Recommendations

- The **NHMRC** (2008) recommends immunisation for all children and adolescents, irrespective of travel, and for all travellers intending to spend a month or more in Central and South America, Africa, Asia or Oceania.
- The **CDC** (2012) recommends HB immunisation for all unvaccinated persons travelling to areas with intermediate to high levels of HB transmission (i.e. HBsAg prevalence ≥2%), all unvaccinated children and adolescents, all who work in healthcare settings, and those who may engage in practices that put them at risk.
- **WHO** (2011) similarly recommends that immunisation be considered for all non-immune individuals travelling to areas with moderate to high risk of infection.
- **Our recommendation**: Given the recommendation for all children and adolescents to be immunised, the high safety and long-term efficacy of the vaccine (better at younger ages), its modest cost, its availability combined with HA, and the common, diverse, unplanned, unpredictable and potentially inapparent nature of risk during travel, we concur with the WHO and CDC recommendations that HB immunisation should be regarded as a 'default' for all travellers to settings of intermediate or high HB prevalence.

For those with indications unrelated to travel, or who plan activities which may involve risk, or who are more likely than most to require health care in high prevalence regions, the case for immunisation is compelling. Because of the increased risk of chronic carriage following infections in early childhood, we regard it as particularly important that all young children be immunised against HB.

HA immunisation will be indicated for almost all travellers for whom HB immunisation is indicated. Whenever protection against both diseases is indicated, we would recommend the use of the combined HA-HB vaccine. Indeed the availability of this vaccine means that immunisation against HA should be considered whenever HB vaccine is indicated, and vice versa.

All children, adolescents, and young adults should receive hepatitis B vaccine if not previously immunised.

Testing for immunity after immunisation

The NHMRC (2008) recommends testing 4–8 weeks after the completion of the vaccine course (whether three or four doses) in the following situations:

- those at significant occupational risk, such as healthcare workers who are frequently exposed to blood and other body substances
- those at risk of severe or complicated disease, for example immunocompromised persons and those with chronic liver disease not due to HB
- those in whom a poor response to immunisation can be expected
- Sexual partners and household contacts of persons chronically infected with HB.

We generally concur with these recommendations. Some studies have shown a delayed serological response and suggest post-vaccination testing be performed from 3 months after completion of the vaccine series. We suggest testing be performed 1–3 months after the last dose, but up to 6 and perhaps 12 months later is satisfactory. We usually check HBsAg, antiHBc and antiHBs at the same time (as well as any other indicated serology). This allows identification of the occasional chronic carrier and of previous exposure and (lifelong) immunity, as well as evaluation of the response to immunisation. On the basis of current evidence and recommendations, further antibody tests are unnecessary once an immunocompetent vaccinee has responded satisfactorily.

An **undetectable antibody level some years after immunisation** is difficult to interpret. Does this indicate a non-response to the vaccine, or has the level simply declined over time, following an initial response? The easiest way to clarify this situation is to give a single vaccine booster dose and check the antibody level at least 2 and preferably 4 weeks later. Those who responded initially will develop a brisk anamnestic booster response in antibody level; non-responders are likely to demonstrate minimal or no rise in antibody levels, and should be managed as such, and offered (generally three) additional vaccine doses.

Post-immunisation antibody testing is best done 1–3 months after the third dose in those at high or occupational risk, at increased risk of severe disease, or who are less likely to respond well to vaccine.

Management of non-responders

A small proportion of immunocompetent patients fail to develop antiHBs in a titre of ≥10 mIU/mL following a standard course of HB vaccine. It has generally been considered that one additional dose will produce a response in 15–25% of

these 'non-responders', and three additional doses in 30–50%; but recent studies suggest that a second three-dose course of Engerix-B results in significantly higher seroprotection rates of up to 75–80%. We recommend that an additional three doses of vaccine (preferably Engerix-B) be given at minimum intervals of 1 month, and antiHBs be measured again 1–2 months after the third supplemental dose. Beyond a total of six vaccine doses, seroprotection may develop in a small number of persons with additional vaccine doses, although the likelihood is low; given the safety of the vaccine, if the patient chooses, we consider providing additional doses up to a maximum of nine.

Those who do not develop seroprotective antibody levels after at least six vaccine doses should be advised that they are susceptible, should minimise the likelihood of exposure, and should seek HBIG within 48 hours of a possible exposure. It is important that chronic carriage has been excluded in such situations.

HB vaccines formulated with novel adjuvants to increase immunogenicity have utility for vaccine non-responders and immunocompromised persons. One such vaccine is licensed in Europe for patients with renal insufficiency. We are not aware that such a vaccine is likely to become available in Australia.

There is no demonstrated need for hepatitis B booster doses in immunocompetent persons who initially seroconvert after immunisation.

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2.6 Influenza

The issue of influenza vaccine is not always sufficiently emphasised to travellers. However, influenza is among the most common vaccine-preventable diseases in travellers, and the severity of the illness means it could easily ruin one's trip and disrupt travel, business, and vacation. Knowledge of a new epidemic in the country to be visited may be sufficient grounds to postpone travel for high-risk individuals. The threat of an influenza pandemic – either from an avian or non-avian influenza strain – has further heightened the perceived risk of influenza among travellers.

Epidemiology

The influenza season in Australia is usually from May to October, and is reversed in the northern hemisphere (usually November–March). The occurrence of influenza may not be seasonal in the tropics: the virus can be isolated year-round and epidemics of disease can occur at various times of the year.

Travellers often frequent crowded settings where transmission is likely. Influenza outbreaks have been well described in relation to travel by train, aircraft, and ship. They have also often been described in travellers to the Hajj. One published cohort study examined the incidence of influenza among 1999 Swiss travellers to subtropical and tropical countries. Among those who reported a febrile illness during or after travel, and who provided both a pre-travel and a post-travel serum sample, seroconversion for influenza virus infection reflected an attack rate of 2.8%, and was confirmed in 1.2%. This study shows that the incidence of influenza among travellers to subtropical and tropical countries is among the greatest of any vaccine-preventable infection (Mutsch 2005).

Vaccine

All influenza virus vaccines currently available in Australia are a purified, inactivated subunit or split virion vaccine. They confer approximately 70% protection against infection for a year, and a lower level of protection for a further year against strains similar to the vaccine strains.

The vaccine formulation is reviewed annually and for each hemisphere so changes can be made to the composition to counter antigenic shifts and

antigenic drifts. Because different influenza virus strains circulate at different times in different parts of the world, with the viruses constantly changing, the current vaccine may not exactly cover all circulating strains. It is, however, likely to cover the predominant and new strains, and offer some protection against strains that are similar, but not identical, to those in the current vaccine.

Note: A new live attenuated vaccine that is administered intranasally is registered in the United States, but is not yet available in Australia.

Dosage and administration

In children under 9 years who are receiving influenza vaccine for the first time, NHMRC (2008) recommends two doses separated by an interval of at least 4 weeks. One dose is sufficient for persons previously exposed to viruses of similar antigenic composition to the strain/s present in the vaccine.

- children 6 months to <3 years – 0.25 mL (two doses)
- children 3–9 years – 0.5 mL (two doses)
- > 9 years – 0.5 mL (one dose)
- Route: IM (this causes fewer local reactions than SC administration).

Adverse effects

Adverse effects following the vaccine are generally mild and include local pain, fever, myalgia, and malaise.

Contraindications and precautions

Egg allergy

The vaccines available in Australia are either split virion or subunit vaccines prepared from virus that has been grown in embryonated eggs. The vaccine was until recently considered to be contraindicated in people with anaphylactic hypersensitivity to eggs. Most egg-allergic children can be safely vaccinated against influenza, according to new allergy guidelines that contrast with existing Australian advice. 'Guidelines for medical practitioners – Influenza vaccination of the egg allergic individual' was published by the Australasian Society of Clinical Immunology and Allergy (ASCIA) in September 2010. This Society is the peak professional body of Clinical Immunologists and Allergists in Australia and New Zealand <www.allergy.org.au>.

The risk of serious allergic reaction to vaccination (anaphylaxis) is very low, estimated at 1 per 4.4 million doses of the influenza vaccine administered. The majority of reported cases of anaphylaxis following influenza vaccination of egg-allergic individuals occurred over 20 years ago, when the amount of egg protein in vaccines was substantially higher. By contrast, the amount of egg ovalbumin present in Australian and New Zealand vaccines in recent years has

been ~1 mg or less/dose (manufacturer data source), substantially less than the estimated 130 mg egg protein taken orally considered likely to trigger reactions in egg allergic patients.

Current evidence is that the vast majority of patients with egg allergy (including anaphylaxis) for whom influenza vaccine is indicated can be vaccinated safely as long as the amount of residual egg ovalbumin is limited to 1 mg or less per dose. This requires checking the egg ovalbumin content for any planned vaccine prior to administration. Since it is not possible in egg-allergic subjects to totally eliminate the very small risk of anaphylaxis to egg protein in the vaccine, vaccines should always be administered in facilities with staff able to recognise and treat anaphylaxis.

We recommend that you consult these guidelines when dealing with patients/travellers with a possible history of egg allergy: <www.allergy.org.au/images/stories/pospapers/ascia_guidelines_influenza_vaccination_egg_allergic_individual_2010.pdf>.

The ASCIA guidelines specifically apply to vaccines containing no more than 1 mg egg ovalbumin per dose. The current egg content of influenza vaccines available in Australia and New Zealand is summarised in a table in the guidelines. Those presenting for immunisation are considered in three potential risk groups: (1) No additional risk, (2) Lower risk, and (3) Higher risk group. For the high risk group the guidelines recommend a split dose protocol with one-tenth of the vaccine dose given first, followed 30 minutes later by the remainder, then another 30-minute supervised wait.

Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) has been associated with influenza vaccination in the northern hemisphere from 1992–94, although a causal role has not been proven. It is advised that the vaccine be given with caution to individuals with a history of GBS.

Age

There is no evidence that influenza vaccine is efficacious in infants <6 months old. Children between 6 months and 5 years of age are more likely to have pronounced reactions to vaccination, and in this group the incidence of febrile reactions is 18%.

Recommendations

This vaccine should be given routinely on an annual basis to:

- **persons ≥65 years of age** – the risk of influenza infection to the elderly is greatest if they also have chronic cardiac or lung disease, and is increased for residents of nursing homes and other chronic care facilities

- **Aboriginal and Torres Strait Islander adults ≥15 years of age** – due to the greatly increased risk of premature death from respiratory disease.

Annual vaccinations should also be considered for individuals in the following groups:

- adults with chronic debilitating disease, especially those with chronic cardiac, pulmonary, renal, neurological, and metabolic disorders
- children with cyanotic congenital heart disease or cystic fibrosis
- adults and children receiving immunosuppressive therapy or with impaired immunity (e.g. from HIV infection)
- staff who care for immunocompromised patients
- residents of nursing homes and other chronic care facilities
- staff of nursing homes and other chronic care facilities
- poultry workers.

Influenza vaccination of all individuals between the age of 50 and 64 years is not recommended according to Australian guidelines, but can be considered.

Children aged 5 years to less than 10 years

There is a strong preference for the use of either Vaxigrip or Influvac in children aged 5 years to less than 10 years. This is based on data which showed no increase in rates of fever or febrile convulsions following administration of either of these vaccines.

Fluvax may still be used in children aged 5 years to less than 10 years when no timely alternative vaccine is available. If Fluvax is administered, parents should be informed of the potential increased risk of fever but that febrile convulsions are rare in this age group.

Fluvax is no longer registered for children <5 years old.

Note: These recommendations are current at time of writing. Any changes will be posted on the website of the Therapeutic Goods Administration: www.tga.gov.au/safety/index.htm.

Travellers

Pre-departure influenza immunisation should be considered for anyone leaving Australia during the local influenza transmission season (so as not to be ill at the time of travel or shortly after).

Pre-departure influenza immunisation should also be offered to anyone leaving Australia who will be exposed during the influenza transmission season at the destination. The risk of infection is particularly elevated in people travelling in large tourist groups such as on cruise ships. Vaccination will decrease the risk of

illness to the individual during the trip, and may also reduce or delay the risk of introducing influenza into Australia upon returning home.

The vaccine offered to Australian residents travelling to the northern hemisphere will be the same vaccine as given during the last southern hemisphere influenza season. It requires that a special effort be made by primary care givers and travel medicine providers to stock influenza vaccine outside the autumn months when it is usually used in Australia.

There is no information available regarding the benefits of revaccinating persons before travel who were already vaccinated in the preceding Australian influenza season (i.e. within the previous 6 months); however they probably do not require revaccination. In contrast, people vaccinated with the previous season's vaccine prior to travel should be revaccinated with the current vaccine before the next Australian influenza season.

Travellers should also be reminded that good personal hygiene and simple measures such as handwashing reduce transmission of respiratory pathogens including the influenza virus.

Chemoprophylaxis or presumptive self-treatment with a neuraminidase inhibitor or amantadine are alternative or additional approaches to the management of influenza in travellers. However, vaccination remains the intervention of choice and these other options should be considered only when the vaccine is contraindicated or was not given before the onset of symptoms.

Influenza is one of the most common vaccine-preventable diseases of travellers.

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Avian influenza

In recent years outbreaks of avian influenza have occurred widely in Asia, including in Japan, South Korea, Vietnam, Thailand, Cambodia, China, Indonesia, and Laos. These outbreaks affected hundreds of millions of chickens, and domestic and wild ducks.

Uncommonly, the virus can cross from infected chickens or ducks directly into humans. Several human cases and deaths have occurred in Vietnam and Thailand. H5N1 is the only strain of the H5 subtype known to have crossed from infected chickens or ducks directly into humans.

The virus is found in bird faeces and respiratory secretions. The risk of direct transmission of H5N1 infection from birds to humans is greatest in persons having close contact with live, infected poultry. There is no evidence of person-to-person transmission of the virus at present.

Potential association with pandemic influenza

One concern is that pigs in parts of China have been infected with the H5N1 strain of avian influenza as well as human influenza H3N2 viruses. The co-circulation of avian, human, and pig viruses in pigs has the potential for exchange of genetic material between these viruses. Reassortment of genes between avian influenza and human influenza viruses could also occur within humans if a person infected with H5N1 becomes co-infected at the same time with human influenza A. Gene exchange could enable the H5N1 virus to acquire human infectivity genes and could give rise to a new influenza virus to which humans have little or no immunity. This new virus could be transmitted from person to person and could trigger a new, pandemic, influenza outbreak.

No vaccine is yet available for avian influenza, and the current vaccine for human influenza does not prevent avian influenza infection in humans. However, influenza vaccination can reduce the chance that a traveller is simultaneously infected with another human influenza strain, prevent morbidity, and reduce concern related to febrile cough illnesses and their potential causes (including avian influenza and SARS).

Advice to travellers

1. Travellers to areas experiencing outbreaks of avian influenza in poultry should avoid contact with live animal markets (which have also been linked with SARS) and poultry farms. Large amounts of the virus are excreted in the droppings from infected birds. Travellers should avoid direct contact with birds, especially chickens and ducks, and particularly ill or dead birds.

2. Avian influenza virus can stick to hair and clothing, and may be inhaled. Thoroughly wash hands, particularly after having contact with poultry and eggs, and undercooked poultry and egg products. Using hot, soapy water and lathering for at least 20 seconds is the single most important procedure for preventing infections.

3. There is as yet no evidence that the virus is transmitted through contaminated food. As a precaution, and until further information is available, it is prudent for travellers to the countries mentioned above not to consume undercooked poultry or raw eggs.

4. Consider influenza vaccination prior to travel. Although this will not protect against avian influenza, it will reduce the chance of simultaneous co-infection with human influenza A, prevent morbidity, and reduce concern and potential disruption to travel plans related to febrile cough illnesses and their potential causes (including avian influenza and SARS).
5. Avoidance of active and passive exposure to tobacco smoke lessens the likelihood and severity of a variety of respiratory infections including influenza.

Pandemic (H1N1) 2009

In 2009 a novel influenza strain, initially called influenza A/2009(H1N1)swl ('swine flu'), and now called pandemic (H1N1) 2009 by WHO, spread in humans. Travellers undoubtedly played a significant role in the rapid transmission of pandemic (H1N1) 2009 globally. It is an influenza A H1N1 virus containing gene segments of viruses from pigs, birds and humans. This strain of influenza is highly contagious but most cases have been under the age of 50 years, a difference from seasonal influenza. The proportion of patients with severe or fatal illness has been small. Very ill patients included pregnant women and previously healthy young individuals, as well as those with co-morbid illnesses such as asthma, morbid obesity, diabetes, immunosuppression and chronic lung diseases. As of the Australian influenza season in 2011, pandemic (H1N1) 2009 has still been circulating in Australia. Therefore this and other influenza strains remain a risk both locally and to travellers.

Advice to travellers

A vaccine to protect against pandemic (H1N1) 2009 is available and has been incorporated (with H3N2 and type B strains) into the regular seasonal influenza vaccine. Therefore all travellers should be considered for vaccination. Travellers should also be reminded about the importance of good personal hygiene to prevent the spread of influenza (including pandemic (H1N1) 2009). For travellers considered at high risk, supply of medication for presumptive self-treatment, such as a neuraminidase inhibitor, can additionally be considered.

2.7 Japanese encephalitis

Japanese encephalitis (JE) is a serious arboviral disease endemic throughout most of Asia and extending into the Pacific region. It may well be the most common form of encephalitis in the world today. In hyperendemic areas, seroprevalence studies indicate nearly universal exposure by adulthood. Consequently, the disease is seen primarily in children.

The JE virus is one of 70 flaviviruses and is closely related to West Nile virus and several flaviviruses found in Australia: Murray Valley encephalitis, Kunjin, Alfuy, Stratford and Kokobera viruses.

Disease

Only about 1 in 250 infections in susceptible individuals in endemic areas is symptomatic. Milder forms of illness may occur, such as a simple febrile illness with headache or aseptic meningitis, but these are usually undiagnosed. The main clinical feature of JE is encephalomyelitis, with widespread involvement of white matter, thalamus, brainstem and spinal cord. Seizures occur in more than 75% of children, whereas adults more commonly present with headache and meningism. The case fatality rate of symptomatic cases is 5–30%, and approximately 60% of survivors will have permanent neurological sequelae, with half of these being left with severe neurological damage.

Elderly persons and pregnant women carry the highest risk of developing symptomatic infection. Infection in pregnancy can result in foetal infection, with undefined consequences, and probably in miscarriage. However, if children <10 years of age develop a symptomatic infection they are more likely to die, or to be impaired if they survive. Prior dengue immunity is associated with a better outcome; concurrent neurocysticercosis (and possibly other conditions that compromise the blood brain barrier) is a risk factor for disease and mortality. The risk of disease may be increased to 1 in 30–50 infections in non-indigenous individuals such as travellers.

Epidemiology

JE is found in virtually every Asian country (Map 2). The virus is transmitted principally by *Culex* mosquitoes, which feed outdoors from dusk till dawn and breed in flooded rice fields, in water around fields, and in marshes. A single rice paddy can produce upwards of 30 000 mosquitoes per day, of which up to 3% may be infected with JE virus. These species have a wide host range that includes domestic animals, birds and humans. Pigs and some wild birds (especially egrets) function as viral amplifiers; infection and illness in humans and horses are incidental to sustaining transmission.

Geographic mobility of the virus is mainly due to migratory birds and wind-blown mosquitoes. Long-term persistence of the virus occurs in some vertebrates. JE is primarily a rural disease, particularly where rice paddies, pigs, birds and humans are in close proximity. It does, however, occur within or at the periphery of many Asian cities. In areas where transmission is intense, antibody positivity may increase by up to 25% per year during childhood.

In several areas, such as Singapore, Japan and Korea, the incidence of JE has declined greatly over the past thirty or forty years in response to urbanisation, reduction in land under cultivation, widespread pesticide use, centralisation of pig production, and, in some areas, widespread use of vaccines and mosquito control efforts. However, incidence is increasing in other areas as a result of deforestation, population growth, spread of agriculture, particularly irrigation, and, possibly, global warming.

Patterns of transmission

There are two main patterns of transmission. In northern temperate regions of China, Siberia, Korea and Japan, transmission occurs in warmer months – May to September. Further south, the season extends from March to October. In tropical areas of South-East Asia and India, seasonal transmission is specific to local monsoonal rain and bird migration patterns, sometimes with two annual peaks. In some tropical areas such as Bali, where the predominant Hindu religion means pigs are abundant, as are rice paddies and birds, transmission is high and year-round. Periodic rice season flooding can have a major influence. See Table 2.7.1, pages 75–77, for risk of JE by country.

JE in Torres Strait and Northern Australia

In April 1995, JE was reported in residents of Badu Island in the Torres Strait (three cases, with two deaths). Widespread, recently introduced infection was documented in a number of outer Torres Strait Islands. Ongoing local transmission became established and has continued in all but one wet season since. Immunisation of the entire population of the outer Torres Strait Islands has resulted in only one additional case occurring, in 1998, in an unimmunised resident. Investigation documented the previously unrecognised presence of JE in the nearby Western Province of Papua New Guinea.

Potentially highly significant from a public health viewpoint is the occurrence, also in 1998, of JE in a man living and working on the western side of Cape York Peninsula. This is the first known case of JE acquired on the Australian mainland. Furthermore, sentinel pigs at the northern tip of Cape York showed evidence of JE for the first time. The potential spread of the virus over much of northern Australia, facilitated by extensive bird and feral pig populations, is of serious concern. Thus far, however, further spread has not been detected.

Japanese encephalitis has been introduced into the Torres Strait and Cape York, with the potential to become much more widespread in Australia.

Travellers and expatriates

From 1973 to 2008, 55 cases have been reported of JE among travellers, the demographic and clinical characteristics of which have recently been reported (Hills 2010). The majority of cases occurred in tourists (33/55; 60%), including three in persons who were visiting friends and relatives (VFRs) and two in students. Expatriates accounted for nine (16%) cases, and six (11%) occurred in soldiers. The type of travel was unknown in seven (13%) of the reported cases. Information on vaccination status was available in 29 travellers, none of whom had been vaccinated. Duration of travel was ≥1 month in 24 (65%) cases. Thirteen travellers had a trip duration <1 month and 10 (77%) of these had travelled for 2–<4 weeks; three (23%) travelled for 10–12 days, highlighting that even

travel for short periods of time may pose a risk for JE. The case-fatality rate was 18% (10 of 55 cases), while 24 (44%) had neurological sequelae. Only 12 (22%) recovered completely.

The estimate of overall risk for JE for the average tourist to endemic areas is <1:1 000 000, but rates can be much higher. In unimmunised intensely exposed soldiers in Asia, rates of 0.005 to 2.1 per 10 000 per week have been documented. These rates are similar to the rates of 0.1 to 1 per 10 000 per week for children in hyperendemic areas.

Accepting the higher estimate, and allowing for transmission in most areas being limited to 5 months of the year, the risk can be estimated as 1 per 200 000 per week of exposure. Cases have occurred in short-term tourists, particularly in Bali, where large numbers of tourists are in close proximity to areas of intense transmission.

Risk factors for acquiring JE infection during travel to Asia

These include:

- travel to a country in which JE occurs (see Table 2.7.1)
- travel during transmission (wet) season
- travel to rural areas
- extended period of travel or residence
- unscreened accommodation and lack of use of permethrin-impregnated bed nets in rural areas
- outdoor activities, especially in twilight and evening
- poor protection against mosquito bites
- lack of immunisation.

Risk factors for developing JE disease

These include:

- advanced age
- neurocysticercosis, possibly other CNS disease compromising blood–brain barrier
- pregnancy – JE acquired in the first and second trimester of pregnancy carries a potential for intrauterine infection and miscarriage.

Vaccines

The most common vaccine previously available in Australia and internationally was manufactured by Biken in Japan (JE-Vax, distributed by Aventis Pasteur).

However, because of the potential for serious adverse reactions to this vaccine (including neurological and severe hypersensitivity reactions), production of the Biken vaccine has been discontinued. A number of vaccine candidates have been developed and two are now licensed in Australia. JESPECT, produced by Intercell Biomedical (Livingston, UK), is a purified inactivated vaccine containing the attenuated SA_{14}-14-2 JE virus. IMOJEV, also based on SA_{14}-14-2 JE virus, is a live attenuated yellow fever-JE chimeric viral vaccine developed by Acambis (UK). It was registered in Australia in the second half of 2010 by Sanofi-Pasteur, and is expected to become available in Australia in 2012.

JESPECT (IXIARO in US and Europe; IC51, Intercell)

Dose

- Each dose is 0.5 mL
- Standard regimen: two doses intramuscularly over a 4 week period.
- The vaccine and diluent should be refrigerated at 2–8°C and should not be frozen.

Immune response and efficacy

The seroconversion rate is 98%, with a geometric mean antibody titre of 244 following two doses of JESPECT (Tauber 2007; Schuller 2008).

Boosters

Antibody titres wane over the first 12–24 months following vaccination. It is therefore recommended that a booster dose be given every 2 years or for those travelling to high-risk destinations a booster be given at 12 months after primary vaccination.

Adverse effects

Mild

- Local: redness and pain swelling in 1%
- Systemic adverse affects are very unlikely to occur. Delayed hypersensitivity reactions, as reported with the Biken JE vaccine, do not occur.

Contraindications and precautions

- JESPECT is not licensed for use in individuals under the age of 18 years. Paediatric studies are currently underway and until these are completed JESPECT cannot be recommended in children.
- JESPECT has not been studied in immunocompromised individuals and pregnant women and consequently cannot be recommended for use in these groups of travellers. However, as JESPECT is an inactivated vaccine it is expected to be safe in immunocompromised subjects. It has not been tested for safety or immunogenicity in pregnant women.

Interactions

A recent Phase III study has shown that the concomitant administration of JESPECT (IC51) and Havrix 1440 is safe and does not lead to interference with the immunogenicity of either vaccine (Kaltenböck 2009).

IMOJEV (JE Chimerivax, JE-CV, Sanofi Pasteur)

Dose

- Each dose is 0.5 mL.
- A single subcutaneous dose.
- The vaccine and diluent should be refrigerated at 2–8°C and should not be frozen.

Immune response and efficacy

The seroconversion rate in adults is 99% with a geometric mean antibody titre of 312 by day 14 after a single dose of IMOJEV and rising to 1392 by day 30. The reactogenicity profile of IMOJEV was significantly better than JE-VAX and comparable to placebo (Torresi 2010). The vaccine has also been tested in children and produces similar high seroconversion rates. 100% of children aged 2 to 5 years and 96% of 12- to 24-month-olds were seroprotected 28 days after vaccination, and the geometric mean antibody titres in these age groups were 2634 and 281 respectively. After 1 year, seroprotection rates in the two age groups were 97% and 84%, and geometric mean antibody titres were 454 and 62.3 respectively (Chokephaibulkit 2010). The vaccine has recently been registered in Australia.

Boosters

Data suggests that a single dose of IMOJEV will provide adequate seroprotection for at least 5 years. However, at present there is insufficient data regarding the long-term durability of antibody response to make a firm recommendation regarding booster doses.

Adverse effects

Mild:

- Local: redness and pain swelling in <1%.
- As with JESPECT, systemic adverse affects and delayed hypersensitivity reactions are very unlikely to occur.

Contraindications and precautions

- IMOJEV is a live attenuated chimeric vaccine and consequently it should not be used in immunocompromised individuals.
- The safety and immunogenicity of the vaccine in pregnancy have not been tested.

Children

IMOJEV has been registered for use from the age of 12 months.

Interactions

No interactions have been described. Prior immunisation against yellow fever does not suppress the response to IMOJEV. Similarly, prior immunisation with IMOJEV does not interfere with the immunogenicity of yellow fever vaccine.

Recommendations

The current recommendations for JE immunisation are unlikely to change regardless of availability of the new generation vaccines.

- **NHMRC (2008)** emphasises the importance of mosquito-bite prevention for all travellers to Asia (and other tropical areas) and of individual risk assessment, recommending JE immunisation for:
  - travellers spending ≥1 month in rural areas of Asia, particularly during the wet season, and/or if considerable outdoor activity is likely, and/or the standard of accommodation is 'suboptimal' [more specifically, not effectively screened or otherwise inaccessible to mosquitoes]
  - all other travellers spending ≥1 year in Asia (except for Singapore), even in urban areas
  - travellers intending to spend ≥1 month in Papua New Guinea, particularly if the travel is during the wet season
  - residents ≥1 year of age of the outer Torres Strait Islands, and those living or working there for a cumulative total of ≥30 days during the wet season (December–May)
  - laboratory personnel who may be exposed to the virus.
- **WHO (2008)** recommends immunisation for travellers with extensive outdoor exposure (e.g. camping, hiking, bicycle tours, outdoor occupational activities, particularly in areas where flooding irrigation is practised) in rural endemic areas during the transmission season. The risk for short-term travellers spending most of their time in urban centres is low and they may not require vaccination.
- **CDC 2010 guidelines** recommend JE vaccine for travellers who plan to spend a month or longer in endemic areas during the JE transmission season. Vaccination is also considered for short-term travellers (<1 month) to endemic areas during the JE transmission season if they plan to travel outside an urban area and their activities will increase the risk of exposure to JE.

JE vaccine is not recommended for short-term travellers whose visits will be restricted to urban areas or times outside the well-defined JE transmission season.

Our practice

We generally concur with the NHMRC recommendations.

- **Stay is less than 1 month**: Immunisation is recommended for those travelling to high-risk areas during periods of peak transmission for that destination.
- **Residing in Asia for more than 3 months**: We recommend immunisation for this duration, and definitely for residence periods ≥6 months, rather than for >1 year.
- **For stays between 1 and 3 months**: Whether immunisation is needed depends on the risk factors outlined earlier. We recommend immunisation for stays ≥1 month during periods of peak transmission. Outside of periods of peak transmission in tropical regions such as South Vietnam we would generally recommend immunisation for stays ≥3 months.
- **Residing in Singapore**: Risk is low; however, expatriates in Singapore often travel extensively in the region outside Singapore. We would recommend immunisation for such mobile individuals based in Asia.

Key readings

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Table 2.7.1 Risk of Japanese encephalitis, by country, region, and season

Country	Affected areas	Transmission season	Comments
Australia	Torres Strait Islands	Probably year-round transmission risk	Localised outbreak in Torres Strait in 1995 and sporadic cases in 1998 in Torres Strait and on mainland Australia at Cape York Peninsula; ongoing risk is currently confined to outer Torres Strait Islands during the wet season (December–May)
Bangladesh	Little data, but probably widespread	Most human cases reported from May to October	Outbreak reported from Tangail District, Dhaka Division; sporadic cases in Rajshahi Division
Bhutan	No data	No data	Assume present
Brunei	Presumed to be endemic countrywide	Presumed year-round transmission	
Burma (Myanmar)	Presumed to be endemic–hyperendemic countrywide	Probably year-round with peaks reported from May to October	Repeated outbreaks in Shan State in Chiang Mai valley
Cambodia	Presumed to be endemic–hyperendemic countrywide	Probably year-round with peaks reported from May to October	Cases reported from 14 provinces including Phnom Penh, Takeo, Kampong, Cham, Battambang, Svay Rieng and Siem Reap
China	Human cases reported from all provinces exept Xizang (Tibet). Hong Kong and Macau are not considered endemic.	Most cases reported from April to October Northern China: May to September Southern China: April to October (Guangxi, Yunnan, Guangdong, and Southern Fujian, Sichuan, Guizhou, Hunan, and Jiangxi provinces) Hong Kong: April to October Taiwan: April to October, with a June peak	Highest rates reported from south-west and south-central provinces. Vaccination not recommended for Beijing or other major cities
East Timor	Presumed to be endemic countrywide	During the rice growing season: two crops in East Timor (September–December and February–May)	High risk on the Maliana Plain (rice paddies, pigs and mosquitoes). In Dili, 65% of the population tested were seropositive for JE by ELISA
India	Reported cases from all states except Dadra, Daman, Diu, Gujarat, Himachal, Jammu, Kashmir, Lakshadweep, Meghalaya, Nagar Haveli, Punjab, Rajasthan, and Sikkim	South India: May to October in Goa; October to January in Tamil Nadu; and August to December in Karnataka. Second peak, April to June in Mandya District Andhra Pradesh: September to December North India: July to December	Highest rates reported from West Bengal, Bihar, Karnataka, Tamil Nadu, Andhra Pradesh, Assam, Uttar Pradesh, Haryana, Kerala, and Goa
Indonesia	Presumed to be endemic throughout the country including Kalimantan, Bali, Nusa, Tenggara, Sulawesi, Maluku, Papua, and Lombok	Probably year-round risk; varies by island; peak risks associated with rainfall, rice cultivation, and presence of pigs. Peak periods of risk: November to March; June and July in some years	Human cases recognised on Bali, Kalimantan, Java, Nasu, Tenggara, Papua, Sumatra, and possibly in Lombok

Table 2.7.1 Risk of Japanese encephalitis, by country, region, and season (Continued)

Country	Affected areas	Transmission season	Comments
Japan*	Rare—sporadic cases on all islands except Hokkaido	Most human cases reported from May to October	Vaccine not routinely recommended for travel to Tokyo and other major cities. Enzootic transmission without human cases observed on Hokkaido.
Korea	• North Korea: No data but assume endemic • South Korea: Sporadic—endemic with occasional outbreaks	May to October	Last major outbreaks in 1982 and 1983. Sporadic cases reported in 1994 and 1998. Vaccine not routinely recommended for travel limited to Seoul or other major cities.
Laos	Presumed to be endemic—hyperendemic countrywide	Presumed to be May to October	
Malaysia	Sporadic—endemic in all states of Peninsula, Sarawak, and probably Sabah	Year-round transmission	Most cases from Penang, Perak, Selangor, Johore, and Sarawak. Vaccine not routinely recommended for travel limited to Kuala Lumpur or other major cities.
Nepal	Hyperendemic in southern lowlands (Terai). Sporadic cases reported from the Kathmandu valley	May to November	Highest rates reported from western Terai districts, including Bankey, Bardia, Dang and Kailali Vaccine not recommended for travellers visiting only high-altitude areas
Pakistan	May be transmitted in central deltas. Cases reported from Karachi	Most cases reported from May to October	Cases reported near Karachi; endemic areas overlap those for West Nile virus. Lower Indus Valley might be an endemic area.
Papua New Guinea	Considered to be possibly throughout the country	Probably year-round risk	Vaccination is recommended for travellers intending to spend a month or more in Papua New Guinea, particularly if travel is during the wet season
Philippines	Presumed to be endemic on all islands	Uncertain; speculations based on locations and agro-ecosystems. West Luzon, Mindoro, Negros, Palawan: April to November Elsewhere: year-round, with greatest risk April to January	Outbreaks described in Nueva Ecija, Luzon, and Manila
Russia	Far Eastern maritime areas south of Khabarousk	Peak period July to September	
Singapore	Rare cases	Year-round transmission, with April peak	Vaccine not routinely recommended
Sri Lanka	Endemic in all but mountainous areas. Periodically epidemic in northern and central provinces	Year-round transmission with a peak in October to January; secondary peak of enzootic transmission May to June	Highest rates reported from Anuradhapura, Gampaha, Kurunegala, Polonnaruwa and Puttalam districts

Table 2.7.1 Risk of Japanese encephalitis, by country, region, and season (Continued)

Country	Affected areas	Transmission season	Comments
Taiwan	Rare sporadic cases	Most cases reported from May to October	Vaccine not routinely recommended for travel limited to Taipei or other major cities
Thailand	Endemic countrywide. Hyperendemic in north; sporadic–endemic in south	Year-round transmission with peaks from May to October	Annual outbreaks in Chiang Mai Valley; sporadic cases in Bangkok suburbs
Vietnam	Endemic–hyperendemic in all provinces	Year-round with peaks from May to October	Highest rates in and near Hanoi and northwestern provinces bordering China
Western Pacific	Two epidemics reported in Guam (1947, 1948) and Saipan (1990)	Uncertain; most cases reported from October to March	Enzootic cycle might not be sustainable; epidemics might follow introductions of virus

- Local JE incidence rates might not accurately reflect risks to non-immune visitors because of high immunisation rates in local populations. Humans are incidental to the transmission cycle. High levels of viral transmission can occur in the absence of human disease.

Based on CDC Health Information for International Travellers 2010.

2.8 Measles, mumps and rubella

Background and epidemiology

Measles vaccine was introduced in Australia in 1970, and endemic measles has been eliminated for several years. Many adults have missed the disease and the vaccine; they are highly susceptible and should be vaccinated before travel. Young adults born before the vaccine was introduced but <50 years of age may also be susceptible; older persons can be assumed to be immune to measles. High-level vaccination coverage is imperative to maintain measles elimination, requiring rates for each new birth cohort of >95% for a single dose and >90% for 2 doses.

Measles is still highly endemic in Asia and Africa, and imported infection has been responsible for several recent outbreaks in Australia. The risk of exposure to rubella in the developing world is also high. All three diseases are more severe in adults than children. All women of child-bearing age should ensure immunity to rubella.

Vaccine

One measles-mumps-rubella (MMR) vaccine is currently available in Australia. A combination vaccine containing measles, mumps, rubella and varicella vaccines (MMRV) will be available in Australia in the near future. A monovalent vaccine is available for rubella where this is specifically required, but monovalent measles and mumps vaccines are no longer available in Australia.

Priorix (MMR) contains live attenuated measles, mumps and rubella viruses. The MMR vaccine viruses are not transmissible and there is no risk of infection from vaccine recipients.

Dosage and administration

- Dose: 0.5 mL given by intramuscular or deep subcutaneous injection.
- Can be given at the same time as other vaccines. If not given simultaneously with other live viral parenteral vaccines, they should be given at least 4 weeks apart.
- Two doses, given at 12 months and 4 years of age. The first dose may be given at 9 months of age if risk of exposure to measles is high. (The second dose may be moved to 18 months of age to provide earlier two-dose protection against measles and to improve vaccine uptake.)

Recommendations

MMR should be offered to anyone born during or since 1966 who has not had two doses of MMR or who has no serological evidence of protection for measles, mumps and rubella. A second dose should be given at least 4 weeks later. If the person is travelling to an endemic area, at least one dose should be offered before the trip.

For infants between 9 and 12 months of age travelling to areas where measles is endemic, MMR should be offered ahead of the schedule. If this is done, another dose should be given at 12 months of age or 4 weeks after the first dose, whichever is later. This should be followed by the standard dose of MMR at 4 years of age.

Healthcare workers and those who work with children should have documented evidence of two doses or serological evidence of protection.

Immune response and efficacy

Immunisation results in seroconversion to all three viruses in over 95% of recipients. A second dose is expected to induce immunity in most vaccine recipients who do not respond to the first dose. Combination MMRV vaccines produce similar rates of seroconversion to all four vaccine components compared with MMR and monovalent varicella vaccines administered separately, though data on the use of MMRV vaccines are not available for those >12 years of age.

Adverse reactions

- Malaise, fever and/or rash may occur after MMR vaccination, most commonly about 7–10 days after vaccination and lasting 2–3 days. High fever (>39.4°C) occurs in up to 15%, and rash occurs in approximately 5% of recipients. The risk for febrile seizures is approximately 1 case per 3000 doses of MMR.
- Encephalopathy occurring 6–15 days after measles vaccine has been reported at a rate of approximately 1 in 2 million doses. This is much less frequent than after natural measles infection.

- Transient lymphadenopathy and arthralgia are rare and occur more commonly in adults.
- Self-limiting thrombocytopenia has been very rarely associated with the rubella or measles component of MMR, occurring in 3–5 per 100 000 doses.
- There has been no scientific evidence to support the claim that MMR vaccination might be causally linked with inflammatory bowel disease and autism, and there is good evidence to refute it.
- Reactions are much less common after the second dose of MMR than after the first dose.

Contraindications and precautions

MMR is contraindicated for:

- those with impaired immunity, including those on high-dose steroids (>2 mg/kg per day prednisolone for >1 week or >1 mg/kg per day for >4 weeks)
- those with anaphylaxis to the vaccine or its components.

If MMR vaccine is given to adult women, pregnancy should be avoided for 28 days, as for rubella vaccine.

Simultaneous administration of other vaccines and blood products

Antibody-containing blood products may interfere with the response to measles vaccination. The effect depends on the amount of immunoglobulin contained in each product, and ranges from 3 to 11 months. Vaccination with MMR or MMRV should be delayed after administration of antibody-containing products (see *The Australian Immunisation Handbook* 9th Edition). After vaccination with MMR or MMRV, immunoglobulin-containing products should not be administered for 3 weeks unless the benefits exceed those of vaccination.

MMR and tuberculin

Mantoux testing is unreliable for at least 4 weeks after the administration of MMR.

Allergy to eggs

Egg allergy, even anaphylaxis, is not a contraindication to vaccination with MMR.

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2.9 Meningococcal infection

Disease

Meningococcal disease is endemic in all countries, with about 500 000 cases occurring each year. However, recurrent epidemics of the disease occur in certain areas.

There are at least 13 distinct serogroups among *Neisseria meningitidis*; serogroups A, B, C, W135 and Y are the major ones associated with disease. Nasopharyngeal colonisation with *N meningitidis* occurs in 5–10% of healthy people, although many of the strains are non-pathogenic. Person-to-person transmission occurs by close contact with respiratory secretions or saliva. Crowding, low humidity, coincidental respiratory tract infections and indoor smoke exposure favour transmission. Epidemics result from a complex combination of host, organism and environmental risk factors.

Epidemiology

Meningococcal serogroup distribution varies by geographic region (see Map 3), age, and over time.

The highest risk occurs in the 'meningitis belt' and surrounding countries of Sub-Saharan Africa (see Map 4).

This region is uniquely susceptible to intense meningococcal epidemics that historically occurred in 8–12 year cycles, lasting 2–3 years. In addition, annual epidemics peak during the dry season (October–June) and decline rapidly with the onset of rain. During non-epidemic periods, the rate of meningococcal disease is roughly 5–10 cases per 100 000 population per year. During epidemics the rate can be as high as 1000 cases per 100 000 (1%) population. Serogroup A predominates, although serogroups C, X, and W135 are also found. Major outbreaks have also occurred in Brazil, northern India, Nepal, and Mongolia. In 2002–03, a major epidemic due to serogroup W135 occurred in Burkina Faso. This was controlled using a trivalent ACW135 polysaccharide vaccine developed rapidly in response to this need. In the last decade or so, the area susceptible to epidemics has expanded to include countries adjacent to the meningitis belt, and countries around the Rift Valley and Great Lakes regions.

In many other countries, the incidence of meningococcal disease has reduced dramatically in recent years. In North and South America, serogroups B and C predominate although serogroup Y causes a substantial proportion of infections in some countries, and W135 is becoming an increasing problem. Most meningococcal disease in Europe is caused by serogroup B strains, particularly in countries such as England that have introduced serogroup C meningococcal conjugate vaccines. Similarly, in Australia and New Zealand, serogroup B predominates. Strain-specific meningococcal B vaccines were developed in Cuba and Norway to control B epidemics. Introduced nationally in 1989, the Cuban vaccine was effective in terminating the epidemic in Cuba and was used subsequently in a number of countries in Latin America, with success depending on the relatedness of major circulating strains to the vaccine strain. In New Zealand, a large serogroup B epidemic began in 1991. A mass immunisation program began in 2004 to protect children and adolescents from the specific strain causing most cases of meningococcal disease in New Zealand. This 'MeNZB' program was very successful, and was stopped in 2008. The vaccine is still available for people considered to be at heightened risk of meningococcal disease. Based on limited data, most disease in Asia is caused by serogroup A and C strains.

The incidence of meningococcal disease in Australia increased steadily over the 1990s to about 3–4 per 100 000. Serogroup B accounted for the majority of cases, but about one-third were caused by serogroup C and the annual incidence rate of disease caused by this serogroup more than doubled during this period. In 2003, a federally funded program of meningococcal C conjugate vaccination began for all infants at 12 months of age, with catch-up immunisation for those up to 20 years of age. The program at 12 months of age is ongoing, and the incidence of meningococcal disease has declined to approximately 1 per 100 000.

Meningococcal disease can affect all age groups. There are two peaks in age distribution: 1–4 years (three times higher than the overall incidence) and 15–19 years (twice the overall incidence).

The overall risk of acquiring meningococcal disease in travellers is low. Risk depends upon the destination and duration of travel, and the age, health status, and closeness and extent of contact between the traveller, the local population, and other travellers. Nevertheless, the high case-fatality rate of 5–10%, even with antibiotic therapy, makes prevention of meningococcal disease an important consideration in at-risk travellers.

Annual Islamic pilgrimage to Mecca and Medina in Saudi Arabia (the Hajj)

The Hajj pilgrimage has been associated with the international spread of meningococcal strains. Timed according to the lunar calendar, more than 2 million Muslims congregate annually in this one-month-long pilgrimage, often

in crowded conditions. Outbreaks of serogroup A meningococcal disease were a problem among pilgrims until 1987, when vaccination was introduced as a requirement for obtaining a Hajj visa. Many were vaccinated with a bivalent serogroup A/C meningococcal polysaccharide vaccine. However, outbreaks of a previously rare strain of serogroup W135 occurred in 2000 and 2001. This strain is hypervirulent, prone to cause disease clusters, and attains a high carriage rate. Cases in returning pilgrims and their families occurred in many countries. Immunisation can protect pilgrims against invasive disease due to this strain, but it may not prevent acquisition of carriage by them. Hence unvaccinated household contacts may acquire infection from returning pilgrims. Meningococcal immunisation requirements enforced by Saudi authorities mean that no international export of meningococcal disease related to the Hajj has been reported since 2004, though serogroups not covered by ACWY vaccine could become a concern.

The risk of international spread of meningococcal disease is lower for Umrah pilgrimage, which is shorter, involves smaller groups of travellers and occurs throughout the year.

Vaccines

There are two types of meningococcal vaccine: the quadrivalent meningococcal polysaccharide vaccines (4vMenPV), and the meningococcal conjugate vaccines. Meningococcal C conjugate vaccines (MenCCV) have been available in Australia since 2001. Two quadrivalent meningococcal vaccines covering serogroups A, C, Y and W135 have become available in Australia since 2010. It is hoped that a globally effective meningococcal B vaccine will become widely available by late 2011 or 2012.

Polysaccharide vaccines (4vMenPV)

Polysaccharide vaccines consist of purified bacterial capsular polysaccharides and are effective against serotypes A, C, Y and W135. They are not effective against other serogroups. As with other polysaccharide vaccines, they are less effective in children under the age of 2 years. Two preparations are available in Australia:

- **Mencevax ACWY** (GlaxoSmithKline)
- **Menomune** (Sanofi Pasteur)

Dosage and administration

- Dose: 0.5 mL for all age groups.
- Given as a single subcutaneous injection (intramuscular injection is not recommended).
- Can be given concurrently with any other vaccines.
- Approved in Australia for those over 2 years of age.

- Anyone (including travellers) for whom optimal meningococcal C protection is recommended or desired should be given MenCCV before being given 4vMenPV. The two should be given at least 2 weeks apart. However ACWY conjugate is a better alternative whenever protection against ACWY serotypes is indicated.

Immune response and efficacy

The vaccine is 85–90% effective against the four serotypes included. It provides effective immunity after 10–14 days in 90% of recipients >2 years of age.

The response is age-related and is least effective in very young children. There is little response to the serogroup C polysaccharide below 18 months, and to the serogroup A polysaccharide below 3 months, with a diminished response between 3 and 11 months of age. In children <2 years of age, efficacy of the Y or W135 components is not known. The high immunogenicity of the serogroup A polysaccharide vaccine in infants and young children is remarkable among plain polysaccharide vaccines, although two doses appear to be needed below 18 months of age.

Antibody levels in early childhood are lower and decay more rapidly than in older children and adults: 67% of children aged 4 years and 95% of those aged 14 years still have protective levels 3 years after vaccination.

Repeated immunisation does not generally produce an accelerated and enhanced antibody response. Immunisation with C polysaccharide vaccine results in reduced antibody responses to subsequent doses of both the C polysaccharide and the serogroup C conjugate vaccine. This 'hyporesponsiveness', seen only for the serogroup C component, occurs in both children and adults, and persists for 4–5 years. It is most marked in infants and young children, and does not occur with the conjugate vaccines. Any significance in terms of clinical protection is not established, but it might be expected to be significant given the importance of antibodies in the protection conferred by polysaccharide vaccines. This adds to the rationale for not using 4vMenPV vaccine unless it is indicated.

The vaccine does not eradicate an established carrier state. An effect on the acquisition of carriage may not occur for up to 7 weeks after immunisation, and is incomplete and transient.

Boosters

A true booster effect does not occur for most polysaccharide vaccines, and 'subsequent doses' is a more appropriate term. There are interesting differences between meningococcal polysaccharides: repeated injections of serogroup A and probably serogroup W135 polysaccharide do elicit booster responses, whereas serogroups C and Y polysaccharides do not. Protective immunity has been shown to persist for 2–5 years, at the shorter end in young children, and at the longer end in older children and adults.

In areas in which disease due to serogroup A or C is highly endemic, revaccination is recommended:

- after 2–3 years for children first immunised at <4 years of age, and for individuals who have deficiencies of properdin or terminal components of complement, or functional or anatomical asplenia
- after 3–5 years for older children and adults.

Adverse effects

Adverse reactions are infrequent and mild, consisting principally of localised erythema that lasts 1–2 days.

Up to 2% of young children develop fever and chills transiently after vaccination, and febrile convulsions occurring 2–4 hours after vaccination have been reported in children <2 years old. Headache, stiff neck and myalgia within 48 hours of vaccination have been reported. However, systemic reactions are uncommon and not severe.

Contraindications and precautions

- **Pregnancy**: Studies of vaccination during pregnancy have not documented any adverse effects on mothers or neonates. Vaccine should be given if there is a significant risk of infection, preferably after the first trimester.
- **Children**: Due to a lack of immunogenicity in children <2 years of age, it is generally not recommended. However, during an outbreak of serogroup A meningococcal infection, children as young as 3 months of age may be vaccinated. In those <24 months, a second dose should be given at least 6 weeks later if there is a continuing risk of infection.

Meningococcal conjugate vaccines

Three different meningococcal C conjugate vaccines (MenCCV) and two quadrivalent ACWY conjugate vaccines are registered in Australia:

- **Meningitec** (Wyeth) consists of meningococcal serogroup C capsular oligosaccharide conjugated to CRM197, a non-toxic variant of diphtheria toxin (the same carrier used in the Hib and pneumococcal conjugate vaccines produced by the same manufacturer). It does not provide reliable protection or boosting against diphtheria.
- **Menjugate Syringe** (CSL Biotherapies/Novartis Vaccines) consists of meningococcal serogroup C capsular oligosaccharide conjugated to CRM197.
- **NeisVac-C** (Baxter Healthcare) consists of meningococcal serogroup C capsular oligosaccharide conjugated to tetanus toxoid protein. It does not give protection against tetanus.
- **Menveo** (Novartis) consists of meningococcal groups A, C, Y, and W135 oligosaccharides conjugated to CRM197 (non-toxic diphtheria toxin

mutant). It is registered for use from 11 years of age in Australia, and from 2 years of age in the US. The FDA is considering licensure down to 2 months of age in the US.

- **Menactra** (Sanofi Pasteur) is another ACWY conjugate vaccine in which the polysaccharides are conjugated to diphtheria toxoid. It is registered for use from 2 years of age in Australia and in the US from 9 months of age. It is unlikely to be licensed for use below 9 months because of its poorer immunogenicity than Menveo in infants.

Dosage and administration

MenCCV

- **Adults and children >1 year of age**: single dose 0.5 mL intramuscular injection (deltoid region).
- **Infants aged 4 to 11 months**: two doses of 0.5 mL intramuscular injection, given at least 4 weeks apart.
- **Infants <4 months**: three doses of 0.5 mL intramuscular injection (anterolateral thigh); first dose not earlier than 6 weeks, and an interval of ≥1 month between doses.
- These vaccines are registered for use in Australia from 6 weeks of age.
- As noted above, whenever optimal meningococcal C protection is recommended or desired, C conjugate vaccine should be given at least 2 weeks before 4vMenPV.

Menveo

- **Adults and children >11 years of age**: single dose 0.5 mL intramuscular injection (deltoid region).
- Currently not licensed for children <11 years of age; however clinical data in children including toddlers and infants appear strong and it is anticipated that the vaccine will be registered for children aged 2–10 years during 2011 and for infants and toddlers in 2012.
- Can be administered concomitantly with dTpa and HPV vaccines.

Menactra

- **Adults and children >2 years of age**: single dose 0.5 mL intramuscular injection (deltoid region).
- Can be administered concomitantly with dTpa, HPV, and injectable typhoid vaccines.

Immune response and efficacy

Seroconversion rates increase with age. Immunogenicity studies have demonstrated close to 100% response following a single dose of vaccine in adults and

toddlers, and >90% response to the three-dose series in infants <1 year. MenCCV conjugated to tetanus toxoid protein is the most immunogenic vaccine, achieving the highest antibody levels, but this has not been shown to be of clinical importance. All vaccines have been shown to be highly effective.

Antibody levels decline rapidly after primary immunisation in children. However, booster responses to 4vMenPV are observed, indicating that the primary series of conjugate vaccine induces immunological memory. Conjugate vaccines reduce meningococcal nasopharyngeal carriage, and thus transmission, more effectively than 4vMenPV. Protection (individual and herd) following immunisation with a conjugate vaccine appears to be more robust and much more persistent than following 4vMenPV.

As noted above, 4vMenPV induces hyporesponsiveness to the meningococcal C component of subsequent doses of both 4vMenPV and C conjugate vaccines, whereas 4vMenPV effectively boosts immunity induced by conjugate vaccine. The issue of hyporesponsiveness is of most potential importance in young children. In adults, the proportion of vaccinees with bactericidal antibody responses above the putative threshold for protection was not altered by prior exposure to one or two doses of polysaccharide vaccine.

The new quadrivalent conjugate vaccines have been compared to 4vMenPV in children 2–10 years of age: a single dose of conjugate ACWY vaccine was well tolerated and induced greater immunogenicity than 4vMenPV. Menveo was also highly immunogenic in infants and toddlers.

Boosters

The duration of protection afforded by conjugate vaccines is currently unknown. Whether a booster dose is required, and if so when, is not currently known, and will depend on the outcome of long-term follow-up studies.

Adverse reactions

Local reactions (pain, redness and swelling) occur in >10% of MenCCV recipients. Fever is noted in up to 30% of toddlers and infants, and about 10% of adults develop a headache. Severe reactions have been reported only rarely. Local and systemic reactions associated with conjugate ACW vaccines occur at rates similar to those observed with the polysaccharide vaccine.

Contraindications and precautions

Pregnancy: It is preferable to avoid all vaccines in the first trimester unless the risk of disease is considered to be significant. However, all available meningococcal vaccines are well-tolerated inactivated vaccines, and safety issues in pregnancy are highly unlikely.

ACWY meningococcal immunisation is required for those from 2 years of age joining the Hajj pilgrimage to Mecca.

Administration of both MenCCV and 4vMenPV

Sometimes both the polysaccharide and the conjugate vaccines are recommended (for example, in asplenic individuals). If MenCCV is given first, AIH recommends an interval of ≥2 weeks before 4vMenPV is given. If 4vMenPV is given first, AIH recommends an interval of 6 months before MenCCV is given. Children below the age of 5 years are not expected to respond well to the C component of 4vMenPV; for them the interval between 4vMenPV and subsequent MenCCV can be reduced to 6 weeks (UK recommendation).

Recommendations

Indications

The need for vaccination should be based on (a) travel destination, (b) risk of exposure, and (c) characteristics of the traveller. The unpredictable nature of epidemics makes definitive guidelines difficult; current information regarding areas of epidemic meningococcal disease should be sought.

Destination

- **The African 'meningitis belt'**: expanded as described above, including Kenya and Tanzania, especially in the dry season (October–June).
- **Saudi Arabia**: Health authorities in Saudi Arabia require documented immunisation with ACWY vaccine of all visitors aged from 2 years arriving for the annual Hajj or Umrah pilgrimages, or for seasonal work. Vaccine is required to have been given <3 years and not <10 days before arrival in Saudi Arabia.
  - The Saudi guidelines for 2010 stipulate that adults and children >2 years of age be given one dose of polysaccharide vaccine (4vMenPV). It is likely that future Saudi requirements will reflect the availability of ACWY conjugate vaccines.
  - Children 3 months to 2 years of age should be given 2 doses of 4vMenPV at least 6 weeks apart.

  Vaccine requirements for Hajj pilgrims are published in the WHO Weekly Epidemiological Record (available on the WHO website).
- Areas with current epidemics: Information regarding current meningococcal disease outbreaks can be sourced from WHO <www.who.int/emc/diseases/meningitis/index.html> and the Centers for Disease Control and Prevention, United States <www.cdc.gov/travel/diseases/menin.htm>.

Risk of exposure

The risk of acquisition increases with the duration of travel (≥1 month) and with the proximity of contact with the local population, especially those planning to live or work with locals. College students and dormitory residents are at increased risk, including in North America.

Characteristics of the traveller

Travellers under the age of 20 years are at the highest risk of acquiring meningococcal meningitis. Also, those with health problems such as asplenia, complement deficiency, alcoholism, or other immune suppressive conditions are at increased risk.

Therefore, in general, the vaccine is recommended for long-term travellers and residents who will be backpacking or living in rural communities of at-risk countries and experiencing close contact with the local population. Vaccination is not necessary for people making short-term business or holiday trips to areas of heightened meningococcal activity if they will have little contact with local populations in crowded conditions.

Which vaccine?

Conjugate vaccines offer substantial advantages over polysaccharide vaccines for encapsulated bacteria like meningococci. These include improved immunogenicity especially in infants, toddlers and young children; stimulation of immune memory; longer duration of protection; lack of hyoresponsiveness with repeat administration; and efficacy in reducing nasopharyngeal carriage, associated with indirect community 'herd' protection through reduced transmission. Therefore, whenever there is a choice of vaccines, we favour a conjugate over polysaccharide meningococcal vaccines. For travellers over 2 years of age, ACWY conjugate vaccine is the preferred vaccine. We expect that these vaccines will become the meningococcal vaccines of choice for travellers of all ages.

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2.10 Pertussis

Background and epidemiology

Pertussis remains a serious, under-recognised and under-reported global health problem. WHO estimates the disease causes about 300 000 deaths annually, the vast majority in early infancy. Pertussis is highly contagious: about 80% of susceptible household contacts acquire the disease. Pertussis infection and disease occur throughout life. Unfortunately, immunity following both disease and immunisation is not durable. Immunisation reduces pertussis transmission, with a consequent benefit in terms of herd immunity. However, in many countries, despite high immunisation rates in children, the incidence of pertussis in adolescents and adults is increasing. This group provides a reservoir of infection for infants too young to be protected by being immunised themselves.

Epidemics tend to occur every 3–4 years. From 1993 to 2005, four epidemics of pertussis occurred in Australia. A total of more than 84 000 cases was reported in this time, an annual incidence of 22.8 to 57.4 cases per 100 000 population. An important study by the Australian Paediatric Surveillance Unit of 140 infants hospitalised with pertussis in 2001 revealed a significant incidence of complications – pneumonia 17%, seizures 4%, encephalopathy 2% – and death in 3%, all in children under 2 months of age. Coughing contacts were recognised in 61% of cases – of these 86% were relatives and 40% were the infant's mother.

There are no data addressing the incidence of pertussis in travellers. However, travel frequently involves relatively close contact with large numbers of people, in transport vehicles and associated settings, and in other public places. In addition, respiratory infections are well documented to be a very frequent source of morbidity in travellers. It therefore seems reasonable to conclude that travellers are generally likely to be at risk of pertussis during travel to a similar or greater extent than at home.

Vaccines

Acellular pertussis vaccines have completely replaced whole cell vaccines in Australia and many other countries. The best of these have efficacy comparable to the best whole cell vaccines, with about two-thirds fewer common and uncommon adverse events. These vaccines have been shown to be safe and effective in adolescents and adults, and make it possible to extend pertussis immunisation beyond the paediatric age group. This is necessary to improve pertussis control, both for adolescents and adults, and for those most at risk of severe and complicated disease – young infants.

The vaccines all contain three or more purified components of *Bordetella pertussis*. These are pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN), fimbrial antigens and agglutinogens. Vaccines are available in

various combinations with the following: diphtheria, tetanus, inactivated polio, hepatitis B and *Haemophilus influenzae* type b vaccines.

DTPa refers to child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines. dTpa refers to formulations for adolescents and adults; these contain substantially lower amounts of diphtheria toxoid and pertussis antigens.

Formulations for children aged <8 years

These all contain 25 µg PT, 25 µg FHA and 8 µg PRN:

- **Infanrix hexa** (GlaxoSmithKline) contains DTPa, hepatitis B (HB), inactivated poliomyelitis vaccine (IPV), *Haemophilus influenzae* type b (Hib)
- **Infanrix-IPV** (GlaxoSmithKline) contains DTPa and IPV
- **Infanrix Penta** (GlaxoSmithKline) contains DTPa, HB and IPV.

Formulations for children aged ≥8 years and adults

These contain 2.5 µg PT, 5 µg FHA, 3 µg PRN, 5 µg pertussis fimbriae (FIM) 2+3:

- **Adacel** (Sanofi Pasteur) contains dTpa.
- **Adacel Polio** (Sanofi Pasteur) contains dTpa and IPV.

These contain 8 µg PT, 8 µg FHA, 2.5 µg PRN:

- **Boostrix** (GlaxoSmithKline) contains dTpa.
- **Boostrix-IPV** (GlaxoSmithKline) contains dTpa-IPV.

Vaccines for paediatric use include larger quantities of diphtheria and tetanus toxoids and pertussis antigens than the respective vaccines for adults. These are recommended for children up to the age of 8.

No monovalent pertussis vaccines are available in Australia.

Dosage, administration and boosters

- Dose: 0.5 mL administered IM.
- Can be given concurrently with any other vaccines.
- Three-dose primary course, with scheduled boosters at 4, 15–17 and 50 years of age.

Australian health departments are recommending that vaccination commence at 6 weeks of age because of an ongoing pertussis epidemic.

Recommendations

dTpa vaccines are recommended for use from 8 years. For adolescents/adults without a previous history of having received pertussis containing vaccine, a

three-dose 'primary' course should be given as dTpa, with two subsequent doses of ADT. dTpa can be used for all primary doses, but this is not routinely recommended as there are no data on the safety, immunogenicity or efficacy of dTpa for primary vaccination.

A single dose of dTpa is recommended for the following:

- Adults (both parents) planning a pregnancy, or as soon as possible after delivery of an infant (preferably before hospital discharge), unless contraindicated. Other adult household members, grandparents and carers of young children should also be offered immunisation.
- Adults working with young children, particularly childcare workers.
- All healthcare workers.
- Instead of dT following a tetanus-prone wound.
- At the age routinely recommended for tetanus and diphtheria booster (50 years); dTpa produces immune responses to tetanus and diphtheria antigens equivalent to ADT, and also provides protection against pertussis.
- Any traveller for whom boosting against diphtheria and tetanus is planned, particularly for those who fall into one of the groups above. The dTpa-IPV combination is useful for travellers who also require booster polio immunisation.

Immune response and efficacy

The various vaccines are highly immunogenic. Protective efficacy against pertussis following primary immunisation is approximately 85%. All adults, irrespective of pertussis immunisation history, respond with a booster response in pertussis antibodies following a single vaccine dose, indicating that by adulthood essentially everyone has either been infected with or immunised against pertussis, or both. dTpa has efficacy of 92–100% against pertussis infection. dTpa vaccines have been shown to be equivalent to ADT in terms of immunogenicity and tolerability.

At present, it is not known for how long a dTpa booster is protective in adolescents or adults, but it would not be expected to be longer than 10 years. Given the relative safety of multiple booster doses of dT in adolescents and adults, and DTPa in children, it is unlikely that repeated dTpa doses would be associated with any safety issues.

Adverse effects

Acellular pertussis vaccines are associated with fever in approximately 20% of recipients and local adverse events in 10%. Febrile convulsions are very infrequently reported following DTPa containing vaccines. The risk is even lower in infants who complete their primary course at 6 months of age. Hypotonic-

hyporesponsive episodes occur in approximately 1 per 100 000 doses of DTPa-containing vaccines given.

Contraindications and precautions

The only true contraindications to acellular pertussis vaccines are anaphylaxis following a previous dose or following any vaccine component. Immunisation should be postponed in those with a major illness or high fever ≥38.5°C. Infants and children known to have active or progressive neurological disease can be safely vaccinated with DTPa-containing vaccines.

Adequate data on dTpa use during pregnancy are not available, but tetanus toxoid is recommended for pregnant women in most developing countries, and is clearly safe. All women who are planning pregnancy should be encouraged to receive a single dose of dTpa before pregnancy; if not given before pregnancy, it should be given to both parents as soon as possible after delivery.

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2.11 Pneumococcal infection

Background and epidemiology

There are approximately 90 *Streptococcus pneumoniae* serotypes, although only a minority cause disease. Some are commonly carried in the upper respiratory tract and can cause otitis media or pneumonia. Others are more frequently associated with invasive pneumococcal disease (IPD), including bacteraemia and meningitis. Common serotypes vary with age and by country. The 10 most

common serotypes cause 62% of disease worldwide; in Australia, seven serotypes cause about 84% of invasive cases. There is limited cross-reactivity among some serotypes.

The highest rates of IPD are seen in children <2 years of age and adults >85 years of age. In Australia the notification rate for IPD is approximately 12 per 100 000 population. Rates are higher in Indigenous Australians. In less developed countries, the incidence of IPD is higher still.

The risk of IPD is highest in patients who have a reduced immune response to pneumococcal capsular antigens, including those with functional or anatomical asplenia, immunoglobulin deficiency, acute nephrotic syndrome, multiple myeloma, HIV/AIDS, chronic renal failure, organ transplantation and lymphoid malignancies. Some other groups of patients develop IPD of higher incidence and/or severity. These include people with chronic cardiovascular or pulmonary disease, diabetes mellitus, alcohol-related problems, cirrhosis, or CSF leak after cranial trauma or surgery, and those who smoke.

Most travellers who do not fall into one of the groups above are not at particular risk of IPD.

Vaccines

There are currently two classes of pneumococcal vaccine available in Australia: polysaccharide, and conjugate. The polysaccharide vaccine contains 23 serotypes (23vPPV). A 7-valent conjugate vaccine (7vPCV) has been available in Australia since 2001. A 13-valent conjugate vaccine (13vPCV) containing the same seven serotypes and an additional six (types 1, 3, 5, 6A, 7F, and 19A) replaced the 7-valent vaccine in the Australian immunisation schedule in July 2011. Conjugate vaccines containing 9, 10 and 11 serotypes are also available.

Pneumococcal polysaccharide vaccine, 23-valent (23vPPV)

Pneumovax 23 (CSL/Merck): 23vPPV contains polysaccharides derived from the 23 serotypes responsible for most IPD cases in adults in Australia. 23vPPV is offered to Indigenous Australians aged ≥50 years and non-Indigenous Australians aged ≥65 years as part of the routine national immunisation program.

Dosage and administration

- Dose: 0.5 mL by SC or IM injection in the opposite limb to other injectable vaccines if possible.
- The vaccine can be given concurrently with any other vaccines.
- If both pneumococcal vaccines are to be given, 7vPCV should be given before 23vPPV. They should be given at least 2 weeks apart.

Immune response and efficacy

At least 90% of recipients of 23vPPV respond with a four-fold rise in type-specific antibody within 2 to 3 weeks. In children <2 years of age, the response is limited to a small number of serotypes unless there has been previous 7vPCV vaccination.

In developing countries, 23vPPV reduces mortality from pneumonia. In developed countries with much lower attack rates of pneumonia, 23vPPV reduces the incidence of IPD, but not non-bacteraemic pneumonia.

Boosters (see table, p. 96)

Revaccination is required after 5 years. Many studies in healthy adults and children show reduced responses to most if not all serotypes following repeated vaccination, consistent with hyporesponsiveness (Poolman 2011; Russell 2010). Therefore, a maximum of three doses (i.e. two revaccinations) of 23vPPV are currently recommended.

A 23vPPV 'booster' dose is recommended following previous 13vPCV:

- at 18–24 months of age, after a primary series of 13vPCV, in Aboriginal and Torres Strait Islander children in the Northern Territory, Queensland, South Australia and Western Australia
- at 4–5 years of age in children at risk of either high incidence or severity of IPD because of underlying medical conditions, following a primary series of 13vPCV.

Adverse effects

Local soreness occurs in around 50%; less than 5% of recipients develop pain or swelling severe enough to limit arm movement. Fever above 39°C occurs in less than 0.5%. Revaccination is not associated with more local adverse events, as had previously been thought.

Contraindications and precautions

23vPPV has been administered in pregnancy without evidence of adverse effects. However, data are limited and deferral of vaccination is recommended unless there is an increased risk of IPD.

Pneumococcal conjugate vaccines

Prevenar 13 (Wyeth): From 2005, 7vPCV was given to all children at 2, 4 and 6 months of age as part of the routine immunisation program. However, serotype replacement, especially with serotype 19A, was observed following the introduction of 7vPCV programs. 13vPCV will provide protection against serotype 19A disease, although there is potential for emergence of other serotypes not included in 13vPCV.

From July 2011, 13vPCV replaced 7vPCV in the infant primary immunisation schedule at 2, 4 and 6 months of age. Children who began their pneumococcal immunisation with 7vPCV can receive 13vPCV for all remaining doses. In addition a supplementary catch-up dose of 13vPCV was offered to all children aged 12 months to 35 months from October 2011 till September 2012.

It is expected that 13vPCV will cover over 60% of serotypes causing IPD among children aged <5 years of age in Australia. In the United States in 2008, a total of 61% of IPD cases among children aged <5 years were attributable to the serotypes covered in 13vPCV, with serotype 19A accounting for 43% of cases. Three of the additional six serotypes in 13vPCV (19A, 7F, and 3) accounted for 99% of IPD cases (Nuorti 2010).

13vPCV confers greater than 95% protective efficacy against IPD due to the serotypes contained in the vaccine. It appears to reduce carriage and to confer herd immunity.

Additional doses of one or both vaccines are also given to those who fall into one of the risk groups mentioned above (see tables, p. 96 and Box, p. 97).

Synflorix (GlaxoSmithKline) is a new 10vPCV approved for immunisation of infants and children aged 6 weeks to 2 years. The carrier protein in the 10vPCV is protein D, a surface protein from non-typeable *Haemophilus influenzae*, a common cause of otitis media.

Dosage and administration

- Dose: 0.5 mL by IM injection in the opposite limb to other injectable vaccines if possible.
- The vaccine can be given concurrently with any other vaccines.
- If both pneumococcal vaccines are to be given, 13vPCV should be given before 23vPPV. They should be given at least 2 weeks apart.

Immune response and efficacy

13vPCV has greater than 95% protective efficacy against IPD due to the serotypes contained in the vaccine. There is also a reduction in incidence of IPD due to non-vaccine serotypes, but the effect is less marked. There is a reduction in non-bacteraemic pneumococcal pneumonia and otitis media. There is evidence for herd immunity.

Boosters

Booster doses of 13vPCV are not generally required, except for those with an underlying medical condition that is associated with a greater risk of severity for IPD (see Box, p. 97); these children should have booster doses at 12 months of age and 4 years of age. Children in at-risk groups who have already received 4 doses of 7vPCV should receive a single dose of 13vPCV.

Table 2.11.1 Pneumococcal vaccination schedule for children ≤9 years of age

Pneumococcal vaccination for children ≤5 years of age		
	13vPCV	**23vPPV**
All healthy children	2, 4, 6 months of age	No
Indigenous children living in NT, Qld, SA and WA only	2, 4, 6 months of age	18–24 months
Children with underlying medical conditions	2, 4, 6, 12 months of age	4–5 years
Pneumococcal vaccination for children >5 and ≤9 years of age with underlying medical conditions		
	13vPCV	**23vPPV**
No history of any pneumococcal vaccination	2 doses, at least 2 months apart	Give 1 dose at least 2 months after last dose of 7vPCV
Has received 7vPCV primary course at 2, 4 and 6 months of age	1 dose	Give 1 dose at least 2 months after last dose of 7vPCV
History of at least two 7vPCV doses, and no 23vPPV	1 dose	Give 1 dose at least 2 months after last dose of 7vPCV
History of 23vPPV, but no 13vPCV	Give 2 doses at least 2 months apart, starting at least 6 months after dose of 23vPPV	

Table 2.11.2 Revaccination with 23vPPV for people ≥10 years of age

Primary dose 23vPPV given to	First 23vPPV revaccination	Second 23vPPV revaccination
Non-Indigenous adults ≥65 years	5 years after first dose	No
Non-Indigenous adults <65 years with underlying chronic medical condition or smoker	5 years after first dose	Either 5 years after first revaccination or at 65 years of age (whichever is later)
Indigenous adults aged ≥50 years	5 years after first dose	No
Indigenous adults aged <50 years with underlying chronic medical condition or smoker	5 years after first dose	Either 5 years after first revaccination or at 50 years of age (whichever is later)
Asplenic individuals	5 years after first dose	Either 5 years after first revaccination or at 50 years of age (for Indigenous adults) or 65 years of age (for non-Indigenous adults), whichever is later

Adverse effects

Local erythema is common, occurring in approximately 10%. Fever also occurs. Prophylactic antipyretic medication is recommended in children who have seizure disorders or a previous history of febrile seizures.

Underlying medical conditions predisposing children ≤9 years of age to IPD

Diseases compromising immune response to pneumococcal infection

- congenital immune deficiency including symptomatic IgG subclass or isolated IgA deficiency (but children who require monthly immunoglobulin infusion are unlikely to benefit from vaccination)
- immunosuppressive therapy (including corticosteroid therapy ≥2 mg/kg per day of prednisolone or equivalent for more than 2 weeks) or radiation therapy, where there is sufficient immune reconstitution for vaccine response to be expected
- compromised splenic function due to sickle haemoglobinopathies, or congenital or acquired asplenia
- haematological malignancies
- HIV infection, before and after development of AIDS
- renal failure, or relapsing or persistent nephrotic syndrome
- Down syndrome.

Anatomical or metabolic abnormalities associated with higher rates or severity of IPD

- cardiac disease associated with cyanosis or cardiac failure
- all premature infants with chronic lung disease
- all infants born at less than 28 weeks gestation
- cystic fibrosis
- insulin-dependent diabetes mellitus
- proven or presumptive cerebrospinal fluid (CSF) leak
- intracranial shunts and cochlear implants.

Contraindications and precautions

Vaccination during pregnancy has not been evaluated for potential harmful effects in animals or humans. Although vaccination is unlikely to result in adverse effects to mother or fetus, it is neither indicated nor recommended.

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2.12 Poliomyelitis

There are three serotypes of poliovirus: 1, 2 and 3. Most infections are inapparent, but some may cause serious damage to the central nervous system. The virus enters the mouth and multiplies in the pharynx and the gastrointestinal cells. It enters the bloodstream via local lymphoid tissue, and may invade the central nervous system and multiply in motor neurons of the anterior horn cells of the spinal cord and the brain stem, resulting in their destruction. Inapparent infection is the most frequent outcome (72%), minor illness (a variable combination of fever, malaise, headache, nausea, vomiting and sore throat for a few days) occurs in 24%, nonparalytic poliomyelitis (aseptic meningitis) occurs in 4%, and paralytic disease in <1% (0.5% in children) of infections in susceptible people. Paralysis may be spinal, bulbar, or mixed spinal–bulbar, and is associated with loss of tendon reflexes and intact sensation. It begins proximally and descends to more distal muscle groups, is usually asymmetric, and while partial or total recovery can be achieved, residual weakness is usually present at 60-day follow-up.

Until the disease is eradicated globally, polio (related to vaccine or wild virus) should be considered in all cases of acute flaccid paralysis, and work-up of such cases should include exclusion of polio, including by viral culture of two stool samples collected at least 24 hours apart and within 14 days of onset of paralysis.

Epidemiology

Dramatic progress has been made towards polio eradication. In 1988, when the global initiative to eradicate polio was launched, there were an estimated

350 000 cases of paralytic polio in 125 countries; in 2003, with much improved surveillance, only about 430 cases were identified, in nine countries. Wild poliovirus type 2 was last detected in India in 1999. Three WHO regions encompassing more than half the world's countries and people have been certified polio-free: the Americas in 1994, the Western Pacific region (including China) in 2000, and the European region in 2002. The four remaining polio-endemic countries are Afghanistan, India, Nigeria, and Pakistan. Of concern is the disruption of polio immunisation programs in northern Nigeria because of cultural taboos, and rumours that the vaccine was tainted in an American plot to sterilise Muslim children. As a result, since late 2002, wild polioviruses genetically linked to northern Nigeria have caused new cases of disease in more than 22 previously polio-free countries, including Benin, Botswana, Burkina Faso, Cameroon, Central African Republic, Chad, Côte d'Ivoire, Ghana, Sudan, Togo, Indonesia and Burma (Myanmar). (See Map 7.) This experience highlights the vulnerability of progress to date and the potential for rapid spread of the virus until it is eradicated everywhere.

The reservoir of infection is humans, most frequently persons with inapparent infection, especially children. Virus is shed from the throat, and from the gastrointestinal tract in the faeces. Faecal shedding may continue for several weeks. Travellers can be important vectors of polio viruses and infect contacts after returning home. At least until polio is eradicated, travellers should continue to maintain immunity against the disease. This is particularly important for travellers to south Asia and Africa. Most travellers will have received a full primary course of vaccine in childhood, but some, particularly the elderly, may have missed being vaccinated.

Inactivated poliomyelitis vaccine (Salk-type or IPV)

The available monovalent IPV is called IPOL (Aventis-Pasteur). The vaccine strain viruses are grown in cultures of Vero cells and inactivated with formaldehyde. Because all IPV now in use is of enhanced potency (eIPV), we simply use 'IPV' to refer to vaccines of enhanced potency. IPV is also contained in numerous combination vaccines that include DTPa, Hib and HB, and therefore are recommended for paediatric use.

Formulations for children aged <8 years:

- DTPa-IPV (Infanrix-IPV)
- DTPa-HB-IPV (Infanrix Penta)
- DTPa-HB-IPV/Hib (Infanrix Hexa)

Formulations for people aged >8 years:

- dTPa-IPV (Boostrix-IPV)
- dTPa-IPV (Adacel Polio)

The availability of dTpa-IPV vaccines provides a useful option for boosting adult travellers.

Dosage and administration

Primary immunisation against polio is recommended at 2, 4 and 6 months, at the same time as DTPa, HB and Hib, with a booster at 4 years. Extra doses of IPV (IPOL) are not needed for babies born prematurely.

For primary immunisation of adults, the NHMRC (2008) recommends three doses of IPV at intervals of 1–2 months. Immunocompromised individuals should receive an additional fourth IPV dose 12 months after the third.

IPV is given by subcutaneous injection, whereas IPV containing vaccines are given by IM injection.

Immune response and efficacy

The administration of two doses of IPV results in the development of protective antibodies in 90–100% of recipients (including children), while this increases to 99–100% after three doses. A single dose of IPV is only 36% effective in preventing the spread of infection in an outbreak setting, while two doses are 89% effective. IPV induces both pharynx and gastrointestinal tract mucosal immunity.

Boosters

All children who received a primary series of IPV alone or a combination of polio vaccines should be given a booster dose at age 4 years (preferably as DTPa-IPV), unless the final dose of the primary series was given after the child turned 4.

For adults a booster doses is only indicated in circumstances of special risk, including:

- travellers to areas or countries where poliomyelitis is epidemic or endemic
- healthcare workers and laboratory workers in possible contact with poliomyelitis cases.

For those exposed to a continuing risk of infection, booster doses are desirable every 10 years.

Adverse effects

Local reactions including redness, pain and discomfort occur in 10–15% of vaccinees on the day following IPV injection and subside within 3 days.

Persons who have had anaphylactic reactions to topically and systemically administered streptomycin and neomycin should not receive IPV.

Live oral poliomyelitis vaccine (Sabin-type or OPV)

OPV is no longer in use in Australia, however OPV and IPV are interchangeable and children who have commenced immunisation with OPV should complete their course of primary vaccination with IPV. OPV is still available in countries attempting to eradicate poliomyelitis and so the vaccine will be discussed here.

Dosage and administration

Three doses given by mouth at 4–8 week intervals. OPV must never be given by injection.

Immune response and efficacy

A single dose of OPV produces immunity in approximately 50% of recipients. A course of three doses will produce long-lasting immunity to all three poliovirus types in >95% of susceptible persons in developed countries. However, only 73% (range 36–99%) and 70% (range 40–99%) of children in developing countries have detectable antibodies for polio virus types 1 and 3 respectively after three doses.

OPV induces a high level of mucosal immunity in the gastrointestinal tract that is superior to that induced by the Salk vaccine. Administration of OPV inhibits concurrent infection with wild polioviruses. The rapid induction of immunity achieved with OPV makes it effective in preventing infection in epidemics and outbreak settings. The number of cases in outbreaks can be reduced by 90% within 2 weeks of administering a single dose of OPV to 80% of a susceptible population.

In immunocompetent persons, the vaccine strain poliovirus normally persists in the faeces for approximately 6 weeks after OPV (usual range: several days to 3 months). In rare immunocompromised individuals, oral vaccine virus can be shed for years.

Adverse effects

Vaccine-associated paralytic poliomyelitis (VAPP) is a rare complication following vaccination with OPV. WHO estimated the risk to be 0.5–3.4 cases per million susceptible children, and the Centers for Disease Control and Prevention (USA) 1 case per 2.4 million doses of OPV (Sutter 2008).

The risk is higher with the first dose, the incidence being 1 case in 750 000 first doses distributed, and 83% of cases of VAPP among vaccine recipients occurred after the first dose of OPV.

The risk is modestly higher in non-immune adults than in children, and higher in immunocompromised individuals, especially patients with abnormalities in B lymphocyte function; the risk is up to 6800-fold higher in patients with agammaglobulinaemia and hypogammaglobulinaemia.

VAPP has also been reported in healthy close contacts of recipients and as community-acquired cases in individuals in whom there had been no known contact with vaccine recipients. The risk among contacts of vaccinees in the US was estimated at 1 in 7.6 million doses of OPV distributed, and 63% of them occurred after the first dose of OPV. Overall, the risk among contacts of vaccinees was 1 in 2.2 million for first doses and 1 in 17.5 million for subsequent doses.

OPV viruses can circulate and, related to rapid genomic evolution, revert to neurovirulence, possibly with increased transmissability. Outbreaks of disease related to such circulating vaccine-derived polioviruses (cVDPVs) have occurred in recent years in Egypt, Haiti, Dominican Republic, the Philippines and Madagascar. Common factors in these outbreak settings have been major gaps in OPV coverage, environmental conditions favouring virus spread, and prior eradication of the corresponding serotype of wild virus. These outbreaks underscore the urgency of reaching polio eradication as soon as possible, and have important implications for the endgame strategy of polio eradication.

Contraindications and precautions

OPV **must not** be given to patients with:

- immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinaemia and agammaglobulinaemia
- altered immune states such as due to HIV infection, leukaemia, lymphoma, and generalised malignancy, from therapy with corticosteroids, alkylating drugs, antimetabolites or radiation.

Persons on corticosteroid therapy

OPV may be given to persons on short-term (<2 weeks), low-to-moderate dose systemic corticosteroids or long-term, alternate-day treatment with low-to-moderate dose short-acting systemic corticosteroids.

Contacts of immunodeficient persons

OPV should not be used in household contacts of an immunodeficient person. Persons who inadvertently receive OPV should avoid close household-type contact with all persons with altered immune status for approximately 2 months.

Pregnancy

It is prudent to avoid OPV in pregnancy unless there is a substantial risk of exposure, although no particular problems have been documented in this setting. IPV-containing vaccines are safe in pregnancy.

Simultaneous administration of other vaccines

OPV can be administered at the same time as **oral typhoid vaccine**. If they are not administered at the same time, administration of OPV should be delayed until 2 weeks after the last dose of oral typhoid vaccine. This is because oral typhoid vaccine produces a strong mucosal interferon response that may reduce the efficacy of OPV. We feel that a purely theoretical concern of potential interaction should not compromise travellers receiving indicated vaccines, even if they are not given concurrently.

OPV can be given at the same time as **other live virus vaccines** or with **immunoglobulin**; otherwise they should ideally, where practicable, be separated by 1 month, except for MMR, which can be given at any time in relation to OPV.

When **BCG** is given to infants, there is no need to delay vaccination with OPV. OPV does not affect tuberculin reactivity as can occur with MMR.

Recommendations for travellers

All travellers (and indeed all persons) should be immune to polio, particularly at this critical period for polio eradication. If there is no history or an uncertain history of immunisation, a primary immunisation course should be administered.

Those receiving primary immunisation should be advised that it takes 2–3 months before solid protection against all three polioviruses is achieved.

Adult boosters are recommended for those at special risk, such as travellers to areas where polio is epidemic or endemic, countries where OPV is still used (because of the risk of VAPP) and healthcare workers in possible contact with cases. This would currently translate to boosters being given for those travelling to parts of Asia and Africa (see Appendix 3). For those at continuing risk, a single booster dose is desirable every 10 years.

The most important need is that travellers, especially those who plan to visit or might visit polio-endemic areas, are known to have been immunised against polio, with a three-dose primary course, and at least one subsequent booster.

IPV must be used for immunocompromised individuals and household contacts of such individuals, including HIV-infected persons.

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2.13 Rabies

Disease

Rabies is a neurotropic viral infection of mammals that can be transmitted to humans. All mammals are believed to be susceptible. Rabies encephalitis is almost invariably fatal, and is conservatively estimated to cause 55 000 human deaths in Asia and Africa each year, the largest number in India. Annual fatality rates are estimated at 2 per 100 000 population in India and 4 per 100 000 in Africa. An estimated 10–12 million people worldwide, mostly in India and China, receive post-exposure prophylaxis (usually with vaccine alone) each year, and it is estimated that current use of post-exposure prophylaxis prevents 330 000 deaths annually, mainly in Asia and Africa. In a recent survey in India, 1.6% of the population experienced a dog bite over a one-year period. Rabid dogs account for more than 98% of deaths in people, and children aged 9–15 years are the most common victims of dog bites.

Although rabies is rare in travellers, rabies risk is not, and travellers should be instructed not to touch, feed, play with or otherwise encourage any domestic or wild mammals in countries where rabies is endemic (Map 8, Table 2.13.1). All travellers to rabies-endemic areas should be aware of the need for prompt post-exposure prophylaxis, even if they have received pre-exposure immunisation.

In areas such as North America and Europe where rabies vaccination of domestic animals is widespread, wild terrestrial carnivores such as raccoons, skunks, foxes and coyotes are important reservoirs. Bats are a major and widespread reservoir of rabies.

Rabies virus comprises genotype 1 of the genus *Lyssavirus*, which includes seven known genotypes. All lyssaviruses can cause rabies. In 1996, a new lyssavirus was identified in bats in Australia. This Australian bat lyssavirus (ABL, genotype 7) is more closely related to classic rabies virus than any of the other genotypes. Two fatal human cases of rabies-like encephalitis were identified in Queensland in 1996 and 1998. ABL has been identified in all four species of Australian fruit bats (flying foxes) and several species of insectivorous bats; all Australian bats should be assumed to potentially be infected with ABL. In laboratory animals, rabies vaccine and rabies immunoglobulin are protective against ABL. Bat lyssavirus infections are found in every continent except Antarctica (Map 9) – thankfully rabies cell culture vaccines effectively cross-neutralise all known strains of bat rabies viruses.

Rabies and other lyssaviruses are usually transmitted to humans via bites or scratches that penetrate the skin, providing the virus in saliva direct access to exposed tissue and nerve endings. The virus may also rarely be inhaled (for example, in bat-infested caves or laboratory settings), or transmitted by organ transplants from patients who died of encephalitis in whom the diagnosis of rabies was missed.

Rabies vaccines are very safe and effective, and should be more widely used for visitors to and residents of rabies-endemic areas. Limiting factors include cost, inadequate awareness of rabies risk, and previous recommendations for regular vaccine booster doses.

Epidemiology

Rabies is common in much of the world, especially the developing world, and occurs in both urban and rural areas. Dogs account for the vast majority (about 98%) of human infections. Most industrialised countries, and Thailand and most countries in Latin America, have dramatically reduced rabies in dogs through immunisation of dogs and reducing the number of stray dogs. However, various wild animals constitute important reservoirs of rabies in different regions. These include bats in most regions, foxes in many areas, mongooses in Asia, Africa and the Caribbean, jackals in Africa, cats and monkeys in Asia, and raccoons and skunks in North America.

WHO's most recent data on rabies-infected countries can be found at: <www.who.int/rabies/rabnet/en>. Other useful information sources include the Pan American Health Organisation <www.paho.org/english/ad/dpc/vp/rabia.htm>, the European Rabies Bulletin <www.rbe.fli.bund.de> and the World Organisation for Animal Health <www.oie.int/eng/en_index.htm>.

Appendix 3 shows a similar list of countries considered to be rabies-free according to various sources (as of December 2010).

Table 2.13.1 Countries and political units reporting no indigenous cases of rabies during 2009[1]

Region	Countries
Africa	Cape Verde, Libya, Mauritius, Réunion, São Tomé and Príncipe, Seychelles
Americas	North: Bermuda, St Pierre and Miquelon Caribbean: Antigua and Barbuda, Aruba, Bahamas, Barbados, Cayman Islands, Dominica, Guadeloupe, Jamaica, Martinique, Montserrat, Netherlands Antilles, St Kitts (St Christopher) and Nevis, St Lucia, St Martin, St Vincent and Grenadines, Turks and Caicos, Virgin Islands (UK and US)
Asia and Middle East	Hong Kong, Japan, Kuwait, Lebanon, Malaysia (Sabah), Qatar, Singapore, United Arab Emirates
Europe	Austria, Belgium, Cyprus, Czech Republic[2], Denmark[2], Finland, Gibraltar, Greece, Iceland, Ireland, Isle of Man, Luxemburg, Netherlands[2], Norway, Portugal, Spain[2] (except Ceuta and Melilla), Sweden, Switzerland, United Kingdom[2]
Oceania[3]	Australia[2], Cook Islands, Fiji, French Polynesia, Guam, Hawaii, Kiribati, Micronesia, New Caledonia, New Zealand, Northern Mariana Islands, Palau, Papua New Guinea, Samoa, Vanuatu

1 Bat rabies may exist in some areas that are reportedly free of rabies in other animals.
2 Bat lyssaviruses are known to exist in these areas that are reportedly free of rabies in other animals.
3 Most of Pacific Oceania is reportedly rabies-free.
Source: CDC Health information for international travel 2012. New York: Oxford University Press, 2012.

The distribution of rabies is not static, and it is important that travellers bitten by mammals obtain authoritative and timely advice regarding the risk of rabies and preventive measures. For example, the island of Bali in Indonesia was previously considered to be free of rabies. However, outbreaks of dog and human rabies first occurred in southern Bali in late 2008 and by one year later had spread to most of the island – ATAGI now recommends rabies post-exposure prophylaxis (PEP) for mammal bites occurring throughout Indonesia, including Bali.

At end 2009, the areas without any rabies or bat *Lyssavirus* risk were limited largely to New Zealand, many Pacific islands (excluding Papua New Guinea and Solomon Islands), Singapore, most of the smaller Caribbean islands, some islands near Africa, Belgium, and Northern Ireland.

Bat rabies is widespread and not always well documented. CDC recommends that bat bites anywhere in the world are an indication for rabies prophylaxis (CDC 2012). WHO (2011) less helpfully states that 'suspect contact' with bats in most countries should be followed by prophylaxis. New Zealand is perhaps the only country where locally acquired rabies has not been described and surveillance is of sufficient quality for us to feel that rabies prophylaxis might reasonably be foregone following a bat bite, subject to current expert local advice. Expert current local advice is important following a mammal bite, especially if rabies prophylaxis is not planned.

Vaccine

Available vaccines

Two rabies vaccines are currently available in Australia:

- **Merieux inactivated rabies vaccine** (Sanofi Pasteur) – in this lyophilised vaccine, the virus has been cultured on human diploid cells and inactivated with beta-propiolactone. When reconstituted, this human diploid cell vaccine (HDCV) turns a rather dramatic pink/purplish colour due to the presence of phenol red. Each 1.0 mL dose contains at least 2.5 IU inactivated rabies virus, neomycin and human serum albumin.
- **Rabipur inactivated rabies virus vaccine** (Novartis Vaccines/CSL Biotherapies). This vaccine is also lyophilised, and contains at least 2.5 IU inactivated rabies virus cultured on purified chick embryo cells and inactivated with beta-propiolactone. This purified chick embryo cell vaccine (PCECV) also contains trace amounts of neomycin, chlortetracycline, amphotericin B and bovine gelatin, and may contain traces of egg protein.

Each 1 mL dose of rabies vaccine costs around $100 when administered in a pre-exposure regimen. Post-exposure immunisation in Australia is paid for by gov-

ernment. However, if post-exposure prophylaxis is required overseas, travellers should expect to pay for it. (While rabies vaccine may be less expensive in many countries than in Australia, rabies immunoglobulin is commonly very difficult to obtain, and when available may cost a few thousand dollars.)

Other cell culture vaccines (CCVs) that may be administered to travellers overseas and that are considered clinically interchangeable include:

- Human diploid cell vaccines (HDCV) (e.g. Imovax, Rabivac)
- Purified chick embryo cell vaccine (PCECV) (e.g. RabAvert, Rabipur)
- Purified Vero cell vaccine (PVRV) (Verorab)
- Purified duck embryo vaccine (PDEV) (Lyssavac N).

If a pre/post-exposure vaccination course has been started overseas using one of the above vaccines, it can be completed using a different cell culture vaccine.

It should be noted that a small number of countries, especially in South-East Asia, continue to produce and use nerve tissue vaccines. These vaccines are less potent, requiring up to 23 daily large injections (e.g. 5 mL), and are associated with an unacceptably high incidence (0.3–0.8 per 1000 vaccinees) of sometimes fatal severe allergic encephalomyelitis. For 20 years WHO has been calling on all countries to replace these hazardous vaccines with modern cell culture vaccines. A number of countries in Asia and Latin America, including India and Nepal, have phased out production and use of nerve tissue vaccines. Travellers needing rabies immunisation should **not** receive nerve tissue vaccines (and seem to be rarely offered them), but rather should travel to a city or country where acceptable cell culture rabies vaccines, and for post-exposure prophylaxis rabies immunoglobulin (RIG), are available.

Rabies is common in much of the developing world and occurs in both urban and rural areas.

Pre-exposure vaccination

Dosage and administration

- **Dose (adults and children)**: three doses, each of 1.0 mL, given over a one month period (days 0, 7, 28). Prolongation of the intervals between doses does not impair the immune response. The third dose can be brought forward to 21 days but no earlier.
- The vaccine **should generally be given intramuscularly**. It should be administered into the deltoid and never into the gluteal region, as the latter results in reduced vaccine immunogenicity. (There are no vaccines for which the gluteal region is an acceptable injection site.) Infants can be given the vaccine in the anterolateral upper thigh.

Immune response and efficacy

Antibodies appear 10–14 days after the first dose. Vaccine doses given during the first 14 days prime the immune system, but at least one dose at 21 days or later is necessary for high titres and for good persistence of antibody.

It is not necessary to check rabies antibody titres after intramuscular vaccination in immunocompetent individuals because three doses of a CCV delivered over 21–28 days induce antibodies in 100% of vaccinees.

The immune response to rabies vaccine is sensitive to immunosuppression due to medical conditions such as HIV or secondary to drugs. For example, 5–10 mg of prednisolone daily may be sufficient to prevent seroconversion. Therefore neutralising antibody titres should be checked following immunisation of immunocompromised individuals. Post-vaccination serology is also worthwhile in persons receiving intradermal vaccine, particularly concurrently with malaria chemoprophylaxis with chloroquine and possibly mefloquine. False-positive HIV antibody tests have uncommonly been reported after rabies immunisation.

Boosters

The generally agreed marker of an adequate immune response to rabies vaccine and correlate of protection is an antibody titre of 0.5 IU/mL, which is usually equivalent to a serum dilution of 1:5. By one year, antibody titres following vaccination generally fall to levels of 1–3.5 IU/mL and may fall below 0.5 IU/mL in up to 20% of subjects after 2 years. However immune memory following pre- or post-exposure rabies immunisation is durable, and a vaccine booster dose is efficient in restoring neutralising antibodies, with 100% of subjects showing a 5-fold rise by day 7.

CDC and NHMRC recommend that individuals at highest, continuous risk – working with live rabies virus (or ABL) in research or in rabies biological production laboratories – should have serum tested for rabies antibodies every 6 months. Such persons are continuously exposed, often to high concentrations of virus, and may have unrecognised non-bite or aerosol exposures. For such persons a booster dose is recommended when their antibody titre falls below 0.5 IU/mL.

Those at frequent risk include veterinarians, animal control and wildlife workers, cavers, and others at ongoing occupational risk in endemic areas, who might have unrecognised non-bite and aerosol exposures. Such persons should have serum samples tested every 2 years, and a booster dose given whenever their antibody level falls below 0.5 IU/mL. Alternatively, a booster can be offered every 2 years.

For those considered at infrequent risk, with exposure to rabies virus nearly always episodic and recognisable, CDC and WHO have for many years not

recommended either serological testing following immunisation or booster immunisation. In CDC recommendations, this includes travellers to rabies endemic areas, and vets and others at occupational risk in areas where rabies is uncommon or rare. However such individuals must be aware of the need for prompt post-exposure boosting with two doses of rabies vaccine 3 days apart (without RIG) should any possible exposure to rabies occur. NHMRC 2008 does not distinguish this third category of infrequent risk, and recommends 2-yearly testing or boosting in all those likely to be exposed to potentially rabid animals in endemic areas, including those in Australia with occupational (and we would add any regular) exposure to bats.

Intradermal vaccination

Rabies vaccines, including both those available in Australia, may also be administered in a 0.1 mL intradermal dose in the same schedule of days 0, 7, and 28. This reduces the cost of vaccination. However, antibody levels are lower and decline more rapidly following intradermal compared with intramuscular immunisation, and the response to subsequent exposure to rabies virus may be slower. In addition, intradermal immunisation should not be used in those taking chloroquine or probably mefloquine for malaria prophylaxis, as this may result in a reduced antibody response, whereas the response is satisfactory when the vaccine is given intramuscularly.

NHMRC strongly recommends that the IM route is preferred for pre-exposure immunisation, and mandatory for ABL prevention, but recognises that reducing costs that would otherwise be prohibitive may assist uptake of rabies immunisation. NHMRC therefore recommends that, while not licensed in Australia, pre-exposure ID rabies immunisation is acceptable provided that:

- ID vaccine is given only by those regularly practising this technique
- the ID route is avoided for anyone with impaired immunity, or taking chloroquine or mefloquine at the time or in the month following
- unused vaccine is discarded at the end of each immunisation session
- rabies antibody is checked 2–3 weeks following completion of the ID vaccine course.

We concur with these recommendations.

Adverse effects

Mild local and systemic symptoms (headache, nausea, abdominal pain, muscle aches, dizziness) may occur, but the vaccine is generally well tolerated. A non life-threatening immune complex-like hypersensitivity reaction is reported in approximately 5% of people 2–21 days following booster doses of HDCV, and occasionally is seen during primary vaccination with HDCV. Symptoms may

include urticaria, pruritis, angioedema, arthralgia, fever, and malaise. These reactions have been attributed to the increased antigenicity conferred on human albumin, present in the HDCV vaccine, by the beta-propiolactone used to inactivate the vaccine virus.

Treatment with analgesics and/or antihistamines can be administered to help control symptoms. Corticosteroids may also be used to control allergic reactions. However, neutralising antibody titres should be checked after cessation of corticosteroid therapy, as it may inhibit antibody response.

Even when adverse effects occur, if at all possible, post-exposure vaccination should not be interrupted.

Contraindications and precautions

There are no absolute contraindications to rabies vaccine for post-exposure prophylaxis for rabies or ABL. The risk of an almost uniformly fatal disease needs to be considered before withholding or interrupting any vaccination course, especially following possible exposure.

If a severe allergic reaction to a rabies vaccine occurs, a different type of CCV should be used. Those with anaphylactic sensitivity to eggs should receive HDCV and not PCECV.

There is no lower age limit for rabies vaccine, though it is infrequently given to children <1 year old who are usually non-ambulatory.

Pregnancy is not a contraindication to rabies vaccine.

Travellers should not accept a nerve tissue vaccine. These are likely to take the form of large volume (e.g. 5 mL) injections scheduled daily for 14–21 days.

Recommendations

The rationale for pre-exposure prophylaxis is to:

- provide protection to people with inapparent or unreported exposure
- simplify post-exposure management, reduce its urgency and eliminate the need for rabies immunoglobulin (RIG) (which is often difficult to obtain and extremely expensive)
- protect individuals for whom post-exposure prophylaxis may be delayed, inadequate or unsafe (e.g. potential use of a nerve tissue vaccine).

The vaccine should be offered to:

- all at occupational risk of mammal contact in rabies-endemic areas, including:
  - animal handlers and hunters

  - wildlife officers
  - zoologists
  - veterinarians and their staff
  - laboratory staff working with rabies virus or mammal specimens or tissues
  - cave explorers
- all likely to have regular contact with bats in areas where rabies or other lyssaviruses may be present
- other individuals who are travelling extensively or living in rabies-endemic countries, particularly countries with canine rabies, and particularly for periods >1 month.

Children are at increased risk of rabies. They are more likely to pat, play with or feed domestic and wild mammals, are more likely than adults to sustain severe, multiple and high-risk bites (in richly innervated tissues and sites closer to the central nervous system: hands, face, head and neck), and may not reliably report mucosal exposures or exposures not associated with significant injury. Children make up a disproportionate number of rabies victims, and rabies in children occurs quite commonly without a known bite or other exposure. The dose of vaccine for children is the same as for adults.

Travellers who **bicycle** around endemic rural areas seem particularly prone to being chased and attacked by dogs.

Aid workers living in endemic countries for long periods, particularly countries where post-exposure prophylaxis may be difficult to obtain, should be immunised; the sending organisation should cover the cost.

We see wider use of rabies vaccine as desirable. The high cost of rabies vaccine is no doubt one obstacle to wider use of pre-exposure rabies prophylaxis. Another is the Australian recommendation of 2-yearly boosters or serological tests for all at continuing risk of exposure. Given long-standing WHO and CDC recommendations that routine testing and booster doses are not necessary for most (immunocompetent) travellers, and the extreme rarity of rabies in persons who have previously received pre-exposure rabies immunisation, we feel comfortable using the CDC and WHO rather than NHMRC recommendations for routine serological testing and vaccine boosters. This has the major practical advantage of avoiding the need for routine rabies vaccine boosters in most immunocompetent travellers who are not at occupational risk of mammal contact or likely to be predictably exposed to bats potentially infected with lyssavirus.

In most countries, CCV rabies vaccines are significantly cheaper than they are in Australia. Thus, immunisation soon after arrival overseas is an option that may be useful for travellers and expatriates.

If an expatriate family wishes to limit rabies pre-exposure immunisation to their members at greatest risk, we would prioritise children over adults who are not at occupational risk of rabies.

Post-exposure treatment

All travellers to rabies-endemic areas – whether or not they have previously been immunised against rabies – should be instructed to avoid patting, playing with, feeding or in any other way putting themselves at risk of exposure to rabies through mammal bites, exposure to mammal saliva on skin lesions or mucous membranes, or significant exposure to bat-infested caves. Post-exposure prophylaxis is extremely effective if all its elements are implemented effectively and promptly. Wounds or exposed mucous membranes should be washed immediately and thoroughly, and then treated with a virucidal antiseptic such as iodine solution. Exposed persons or their carers should seek competent medical attention, and if assessed to be at risk should receive post-exposure vaccine (a cell culture vaccine) and in addition, if not previously adequately immunised, rabies immunoglobulin (RIG) as soon as possible (preferably within 48 hours).

Given the difficulty of access and the high cost of post-exposure rabies prophylaxis (particularly RIG) in many countries, travellers should be prepared to travel to a major centre or another country, or return to Australia, in order to access optimal post-exposure prophylaxis.

Other aspects of wound care – such as tetanus prophylaxis and antibiotics – should also be administered as appropriate. Whenever possible, rabies-prone bite wounds should not be sutured for at least several hours and preferably not for a few days.

It must be emphasised to travellers that immediate and thorough washing of the wound with soap and water is vital, regardless of whether prior vaccination has been instituted. Agents such as povidone-iodine are virucidal and when available should also be used to clean the wound.

All travellers to rabies-endemic areas should avoid contact with mammals, promptly and thoroughly wash bites or saliva-contaminated areas, and seek post-exposure immunisation within 48 hours.

Provided no delays are involved, potential rabies exposures should generally be managed by those experienced in their management. Health staff facing an issue of rabies risk should have a low threshold for seeking advice from their state/territory public health authority and/or an infectious diseases service.

Post-exposure treatment should generally be given following a bite, scratch or mucous membrane exposure from a bat in any country, including Australia.

In the absence of vaccine shortage, post-exposure immunisation should be given regardless of the time interval since exposure.

Persons previously adequately immunised

Individuals with a reliable history of pre- or post-exposure rabies immunisation with cell culture rabies vaccine, or previously immunised with any other type of vaccine and with a documented adequate antibody response, should be given two booster doses as follows:

- **Dose**: two doses of a rabies cell culture vaccine, 1 mL
- **Administration**: Intramuscularly (deltoid, or lateral thigh in infants; never gluteal), one each on days 0 and 3.

This should be done irrespective of the length of time since the previous vaccination and regardless of the antibody levels (if known). Thus, even if an individual is known to have an antibody level of >0.5 IU/mL at the time of potential exposure, they should still be given two booster doses of vaccine. No RIG is required.

Individuals with a history of pre- or post-exposure prophylaxis with a nerve tissue vaccine, or with an uncertain immunisation history and no documented immunity, should receive a complete four vaccine dose post-exposure course together with RIG.

Persons not previously adequately immunised

Give rabies immunoglobulin (RIG) plus four doses of rabies vaccine.

RIG

- **Dose**: RIG 20 IU/kg body weight
- **Administration**: All or as much as possible of the RIG dose should be infiltrated around and into the wound or wounds, even if the lesion has begun to heal. Care is needed when injecting into tissue compartments (e.g. into a finger). All wounds should be irrigated/infiltrated. Any remaining RIG should be injected intramuscularly at a site distant from the site of vaccine inoculation.

RIG is in limited supply globally, is expensive and is often not available in developing countries.

The total recommended dose of RIG must not be exceeded, as it may reduce the efficacy of the vaccine. If the calculated dose of RIG is insufficient to infiltrate all wounds, sterile saline can be used to dilute it to a volume sufficient to enable thorough infiltration.

If RIG is unobtainable when the first dose of vaccine is given, it may be given up to day 7. After that time, it is unnecessary to give RIG, as vaccine-induced antibodies will have begun to form.

Equine RIG or fractions of ERIG are used in many developing countries and are acceptable and should be used if human RIG is not available. Modern purified equine RIG is associated with a low (<1–2%) rate of serum sickness-type allergic reactions, which are readily manageable.

Rabies vaccine

In June 2009, the US Advisory Committee on Immunization Practices approved the use of HDCV and PCECV in a four-dose post-exposure series (on days 0, 3, 7 and 14, i.e. omitting a previously-recommended fifth dose on day 28–30). This recommendation has now been adopted by ATAGI; except five vaccine doses continue to be recommended for those with immune impairment, whether from disease or treatment, and following exposure risk to Australian bat lyssavirus.

- **Dose**: four doses of HDCV 1 mL, one each on days 0, 3, 7, and 14; if indicated, a fifth dose on day 28
- **Administration**: into deltoid area by IM or SC injection.

If a course of post-exposure vaccination has been started overseas using a cell culture vaccine, the standard post-exposure regimen should be completed in Australia.

If the post-exposure vaccine used overseas was a non-cell culture vaccine (nerve-tissue vaccine), the exposed traveller should be given a complete post-exposure regimen using a cell culture vaccine.

The incubation period of rabies is generally 20–60 days, however periods of >1 year have been reported in humans. Thus, when a documented or likely exposure has occurred, post-exposure prophylaxis is indicated regardless of the length of the delay, provided clinical signs of rabies are not present.

It is concerning that many people at risk only present for post-exposure prophylaxis many days, weeks or occasionally months after possible exposure to rabies. While post-exposure prophylaxis is indicated regardless of the time interval that has elapsed since the possible exposure, the effectiveness of post-exposure prophylaxis is almost 100% if all elements – wound care, vaccine and RIG if indicated – are applied within 48 hours, and declines if any of these elements are omitted or delayed.

Vaccine and RIG shortages

Shortages of rabies vaccines and RIG seem to occur more frequently than with other vaccines. One contributing factor is that global production of RIG routinely falls short of requirements.

Table 2.13.1 Pre- and post-exposure rabies immunisation schedules

Immunisation, route	Days doses are given	Comments
Pre-exposure		
IM	0, 7 and 28	Standard regimen 3rd dose can if necessary be brought forward to day 21
ID	0, 7 and 28	A less favoured alternative appropriate for experienced clinics and selected patients, preferably with follow-up serology – see text
Booster doses	Single dose 6 monthly for individuals at highest risk; 2-yearly booster or antibody titre and boost when level falls below 0.5 IU/mL for those at frequent risk; see text	The authors follow CDC and WHO recommendations in not recommending routine rabies vaccine boosters for immunocompetent persons who are not at occupational risk of rabies exposure and do not have regular contact with bats in any country, including Australia. NHMRC 2008 continues to recommend 2-yearly boosting or testing and boosting if the titre falls below 0.5IU/mL for 'those likely to be exposed to potentially rabid animals in endemic countries', (as well as those with occupational exposures to bats in Australia).
Post-exposure (if previously unimmunised)*		
IM	0, 3, 7, and 14, plus RIG day 0	RIG should not be used more than 7 days after a first dose of a cell culture rabies vaccine (CCRV). Post-exposure prophylaxis commenced with one CCRV (e.g. overseas) can be continued with a different CCRV. A fifth dose on day 28 should be given in the case of bat exposure or impaired immunity.
Post-exposure (if previously immunised with cell culture vaccine)		
IM	0, 3	Those previously immunised with a nerve tissue rabies vaccine, or with a rabies vaccine of unknown or uncertain type, should only be managed as if previously immunised if they have a documented history of a positive antibody response (>0.5 IU/mL).

* A variety of different IM and ID regimens are approved by WHO for post-exposure prophylaxis (PEP) and used in a number of countries, such as India, Philippines, Sri Lanka and Thailand. Some regimens should only be used with particular vaccines. All involve repeated doses over at least 21 days; some involve multiple simultaneous doses injected at different sites at the first contact. The intradermal regimens are assisting to make rabies PEP more widely available and affordable by reducing the volume of vaccine required.

When rabies vaccine is in short supply, post-exposure treatment should be prioritised over pre-exposure immunisation, pre-exposure immunisation should be focused on those at greatest risk, and the vaccine-sparing aspects of intradermal immunisation of groups of vaccinees become most helpful.

When RIG supply reaches critical levels, consultation with the relevant state/territory health department and referral of patients exposed to risk of rabies to infectious diseases services become even more important. When RIG supply is inadequate and needs to be prioritised for those at greatest risk, RIG may **not** be recommended for possible exposures meeting the following criteria:

- Exposures >12 months previously, where the risk of rabies has become very small; or

- Where the result of testing the involved animal is available within 48 hours of the exposure, and the result is negative; or
- Where a scratch and not a bite occurred and **all** of the following apply:
  - The scratch was not on the head or neck
  - The animal was not an insectivorous bat
  - The animal was behaving normally at the time of the scratch
- The person involved is immunocompetent.

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2.14 Rotavirus infection

Background and epidemiology

Rotavirus is the most common cause of severe dehydrating gastroenteritis in infants and young children in both developed and developing countries. Rotavirus infections are often more severe than other common causes of diarrhoea, and are more likely to be associated with dehydration and hospitalisation. Individuals may have repeated rotavirus infections throughout life, but it is the first infection, usually between 3 months and 3 years of age, that is most likely to

cause severe diarrhoea and dehydration. After a single natural infection, 40% of children are protected against any subsequent infection with rotavirus, 75% are protected against diarrhoea from a subsequent rotavirus infection, and almost 90% are protected against severe diarrhoea.

In Australia, there are approximately 10 000 hospitalisations per year due to rotavirus in children <5 years of age. More than twice this number require emergency department care for rotavirus infection. There is little mortality associated with rotavirus infection in Australia: one death attributed to rotavirus per year. Morbidity and mortality figures for developing countries are much higher.

Vaccines

There are two oral rotavirus vaccines available in Australia, both of which are live attenuated vaccines:

- **Rotarix** (GlaxoSmithKline) contains one strain of attenuated human rotavirus (G1P1[8] strain).
- **RotaTeq** (CSL/Merck) is a pentavalent vaccine containing five human–bovine rotavirus reassortants with the human serotypes G1, G2, G3, G4, and P1[8] and the bovine serotypes G6 and P7.

Dosage and administration

Rotarix

- Dose: 1 mL administered orally (requires reconstitution).
- Can be given concurrently with any other vaccines.
- Two-dose course (at 2 and 4 months of age).

RotaTeq

- Dose: 2 mL administered orally.
- Can be given concurrently with any other vaccines.
- Three-dose course (at 2, 4 and 6 months of age).

There are upper age limits for administration of both vaccines (see Table 2.14.1).

Recommendations

Rotavirus vaccine is part of the Australian Standard Vaccination Schedule (see Table 2.1.1). There are no specific recommendations for travellers.

Immune response and efficacy

A course of either vaccine prevents rotavirus gastroenteritis of any severity in approximately 70% of recipients over the following 1–2 years. The efficacy

Table 2.14.1 Age limits for dosing of oral rotavirus vaccines

	Doses	Age of routine oral administration	Age limits for dosing (weeks)			Minimum interval between doses
			1st dose	2nd dose	3rd dose	
Rotarix	2 oral doses	2 and 4 months	6–14[1]	10–24[1]	None	4 weeks
RotaTeq	3 oral doses	2, 4 and 6 months	6–12[2]	10–32[2]	14–32[2]	4 weeks

1 Upper age limits for administration of Rotarix: first dose 14.9 weeks, second dose 24.9 weeks
2 Upper age limits for administration of RotaTeq: first dose 12.9 weeks, second dose 28 weeks, third dose 32.9 weeks

against severe rotavirus gastroenteritis and against hospitalisation for rotavirus gastroenteritis is approximately 90%.

Adverse effects

The vaccines are well tolerated with few adverse effects.

A previous (tetravalent rhesus-reassortant) rotavirus vaccine was associated with an apparent increased risk of intussusception in vaccine recipients (approximately 1 in 10 000). This risk appeared to be greater if the vaccine was given after 3 months of age. Although the current rotavirus vaccines differ in composition, there was sufficient concern about the risk of intussusception that trials of Rotarix and RotaTeq have been restricted to infants under 6 months of age. Recent studies suggest a small increased risk of intussusception in infants following rotavirus vaccine. This increased risk appears to occur mainly in the 3 to 7 days following the first dose (Patel 2011). This risk is substantially smaller than was observed with earlier rotavirus vaccines.

Contraindications and precautions

Infants with moderate to severe acute gastroenteritis should not be vaccinated until after recovery from their acute illness. As with other vaccines, infants with any moderate to severe illness should be immunised after recovery. There are no studies of the safety or efficacy of either rotavirus vaccine in infants with impaired immunity, but there are theoretical concerns that gastrointestinal disease associated with the vaccine virus could occur.

The vaccine virus may be shed in stool and there is a small risk of transmission to contacts. Contacts with impaired immunity are those most likely to be at increased risk, though the risk of being exposed to disease from natural infection is considered to be higher.

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2.15 Tick-borne encephalitis

Tick-borne encephalitis (TBE) is a serious viral infection of the central nervous system. It is prevalent over a broad sweep of Europe and Asia, and travellers may ask about it. More often, travellers may be unaware of the disease. Those who are assessed as being at significant risk should be advised of the disease, its prevention, and the availability of safe and effective vaccines. No vaccine is licensed in Australia, but at time of writing Baxter keep a small stock of vaccine in Australia for use under the Special Access Scheme. TBE vaccine is the largest-selling vaccine in the private market in Europe (about 80 million doses administered since 1980). Thus far, Austria is the only country to have embarked on a national TBE immunisation program.

The disease has previously been referred to by a variety of other names, including Central European encephalitis, Far Eastern encephalitis, and Russian spring–summer encephalitis.

Disease

TBE virus is a flavivirus transmitted to humans by the bite of infected ticks, most often *Ixodes* spp. Three subtypes are recognised: European, Siberian, and Far Eastern. While there are ecological and clinical differences, the three subtypes are closely related antigenically and vaccines are effective against all subtypes.

The virus circulates mostly in small wild animals, chiefly rodents, but also infects large mammals such as deer and goats. Tick bites in humans usually occur on the hair-covered parts of the head, ears, arms and knees, or on hands and feet. Due to the anaesthetising effect of the saliva, tick bites cause no pain and may not be noticed, so up to 30% of TBE patients do not remember being bitten by a tick. Unfortunately the virus is transmitted from the saliva of an infected tick within minutes of the bite, so early removal of ticks, while recommended, has not been shown to reduce the likelihood of disease. People may also be infected by consuming unpasteurised dairy products from infected goats, sheep or cows.

TBE causes acute meningoencephalitis with or without myelitis. About 70% of infections are thought to be asymptomatic. Illness may be monophasic or more

usually biphasic. In the latter, a flu-like illness develops 2–28 days (generally 7–14 days) after the bite of an infected tick. After an afebrile period of 4–10 days, a second febrile phase develops, associated with meningitis or meningoencephalitis, and about one-third of those who develop the second phase of illness develop full-blown encephalitis, including paralysis (especially of the upper limbs), coma, and pyramidal tract signs.

Children and adolescents tend to present with meningitis; paresis and sequelae are less common in this group. European subtype disease is more serious in older patients: those >40 years are more likely to suffer the encephalitic form, and those >60 years are more likely to develop severe disease resulting in death or permanent sequelae. In contrast, the Far Eastern form tends to be more severe in children. The Far Eastern subtype is associated with more severe disease generally and higher risk of sequelae (30–80% of survivors) than the Siberian or European subtypes. The case fatality rate for the European subtype is 1–2%, for the Siberian subtype 6–8%, and up to 20–40% for the Far Eastern subtype, though reporting and clinical care differences may contribute to this disparity.

Epidemiology

More than 10 000 cases of TBE are reported each year, and the number is growing. TBE is second to Japanese encephalitis among neurotropic flaviviruses in terms of morbidity. The ticks live in wooded areas (mostly in transitional zones between different forms of vegetation, such as along the edges of wooded areas), in young forest plantations with undergrowth, and along streams or in river meadows. These ticks are found on grasses and shrubs up to half a metre above the ground. Humans pick up the ticks through contact with infested undergrowth and grasses. The distribution of TBE is locally patchy. In central Europe, two peaks of TBE are seen: June–July, and September–October.

TBE is found in almost the entire southern part of the temperate Eurasian forest belt from Alsace-Lorraine in eastern France in the west, from Albania in the south to Finland in the north in Europe, to eastern Siberia, northern Mongolia, northern and eastern China, South Korea, and Hokkaido in Japan in the east. In some areas of Russia, Scandinavia and Germany, population prevalence of TBE antibody is between 40% and 100%, though generally in endemic areas in the pre-immunisation era it was 1–20%. The highest incidences are currently reported in the Baltic states (Estonia, Latvia, Lithuania), Russia (particularly in the north-west and in Siberia) and Slovenia. Incidence is also high in the Czech Republic, Germany, Hungary, Poland, Sweden and Switzerland. No cases have been reported in Belgium, Ireland, Luxembourg, Netherlands, Portugal, Spain or the United Kingdom.

In recent decades, the reported incidence has increased substantially in Lithuania and Germany, and infection is now being reported from areas not previously known to be endemic in Germany, Lithuania, several regions in Russia, Scandinavia and Switzerland. Since 1980, Austria has had a national TBE

immunisation program which reached 88% coverage of the whole population by 2005 and has led to a 90% fall in disease incidence. Despite this it should be noted that the risk for an unimmunised person in Austria has probably increased over this time. Decline of cases along the southern edge of its range, upward migration in altitude (from <800 to about 1500 m altitude) in Austria, the Czech Republic and Slovenia, and northward movement of TBE and its tick vector, particularly in Sweden, have been associated with a warming climate.

High-risk activities include agriculture, forestry, hiking, camping, fishing, outdoor sports, mushroom and berry collecting, military activities, and any other activities in the warmer months of the year (generally April to November) that bring people to forest and meadow areas and into contact with *Ixodes* ticks. TBE currently rarely occurs above 1400 m altitude or in urban areas. In endemic areas, generally fewer than 5% of ticks, but in Siberia up to 40%, may harbour the virus.

While TBE is a serious disease, and cases may have occurred overseas or been undiagnosed or unreported, we are not aware of any published or anecdotal reports of TBE in Australian travellers. The overall risk of TBE in unimmunised visitors to an endemic area during the transmission season has been estimated at 1 case per 10 000 person-months of exposure.

Austrian and German vaccines

Two TBE vaccines are available in western Europe (Encepur, Novartis Vaccines, Marburg, Germany, and FSME-IMMUN, Baxter AG, Vienna, Austria). For both vaccines, virus is grown in chick embryo cells, inactivated with formaldehyde, and adjuvanted with aluminium hydroxide. The vaccines use different but almost identical viral strains. The Baxter vaccine contains human serum albumin as a stabiliser. The current formulation of the Novartis vaccine contains only sucrose as a stabiliser (bovine gelatin was removed after being associated with allergic reactions). Both manufacturers provide adult (0.5 mL) and paediatric (0.25 mL) formulations, the latter containing half the adult dose and indicated from 1 year of age.

Neither vaccine is registered in Australia at time of writing, but both are widely available in Europe and some other countries (e.g. FSME-IMMUN adult formulation is licensed in Canada). Baxter maintains a small stock of FSME-IMMUN in Australia which can be accessed through the Special Access Scheme on a named patient basis.

Dosage and administration

- Standard schedule: three doses given intramuscularly at 0, 1–3 months, and 9–12 months.
- Accelerated schedule: three doses given at 0, 7 and 21 days for Encepur with a first booster at 12–18 months, and 0, 14 days and 5–12 months with first

booster at 3 years for FSME-IMMUN. The accelerated schedules are much more useful for travellers.

Immune response and efficacy

Seroconversion rates of 98–100% are achieved in adults and children with the standard schedule. With the accelerated regimen for FSME-IMMUN, seropositivity developed rapidly: it was 0 at day 0, 89.3% at day 3, 96.4% at day 7, 98.2% at day 14 and 100% at days 21 and 42. For Encepur, seroconversion rates at 6 weeks after the first dose of an accelerated course were reported to be 100% for both adults and children, though the antibody response is poorer over the age of 60 years. Antibody titres achieved following immunisation are similar to those in convalescent sera.

TBE vaccines are highly effective; effectiveness in the Austrian national program was estimated to be over 98% after two or three vaccine doses between 1994 and 2001. There is evidence of good cross-protection for both vaccines against all three viral subtypes.

Therefore, on the basis of both immune response and effectiveness data, although three doses are recommended, two doses are likely to provide good protection over at least one summer season.

In persons with pre-existing antibodies to yellow fever and dengue (both flaviviruses), some interference in the immune response to TBE vaccine occurs, with TBE-neutralising antibodies being induced only after the third vaccine dose. We know of no data regarding TBE immunisation of subjects previously immunised against Japanese encephalitis, but pre-exising antibodies to TBE interfere with the antibody response to JE vaccine.

Booster

A booster is recommended initially at 3 years for FSME-IMMUN, at 12–18 months for Encepur, and then 5-yearly for those <50 years of age and 3-yearly for those ≥50 for both vaccines. These recommendations are probably excessive, and several countries are reviewing booster recommendations. Currently Switzerland is the only country to recommend a longer – 10-year – interval for first and subsequent boosters.

The two vaccines seem to be interchangeable after a primary immune response.

Adverse effects

Generally mild and unremarkable local and systemic adverse events (including fever in up to 15–20% and headache) can accompany TBE immunisation; these occur somewhat more frequently after the first than subsequent doses, and fever is more common in young children.

Russian and Chinese vaccines

Two vaccines against TBE are manufactured in Russia – TBE-Moscow and EnceVir. Both are modern tissue culture vaccines of assured quality, stabilised with human serum albumin, and licensed in Russia and neighbouring countries for use in individuals ≥3 years of age. More than 25 million people have received the TBE-Moscow vaccine. A mass immunisation program initiated in the Sverdlovsk region of Russia in 1996, mostly using TBE-Moscow, reduced the incidence of disease almost 10-fold. However, large-scale randomised controlled trials addressing the safety of these vaccines have not been published, and in both 2010 and 2011 some lots of Encevir were withdrawn after being associated with a high frequency (up to 19%) of high fever and allergic reactions, particularly in children. This vaccine is currently not recommended in children aged 3–17 years.

We feel a Russian vaccine, preferably TBE-Moscow, is an acceptable alternative if the Austrian or German vaccines are unavailable. We would not favour travellers accessing a Chinese vaccine used in northern regions of China, as data on this vaccine have not been published in international journals.

Recommendations

WHO recommends that where the disease is highly endemic (≥5 cases per 100 000 population per year) immunisation should be offered routinely to all age groups. WHO recommends immunisation of travellers whose visits will include extensive outdoor activities in endemic areas.

We recommend TBE immunisation for travellers visiting endemic areas in Europe and Asia from late spring to early autumn, April–November, and substantially involved in:

- recreational activities involving high risk of tick exposure in forested and meadow areas (e.g. farming, camping, hiking, jogging, mountain biking, orienteering, rogaining, hunting, gathering mushrooms or berries)
- working in forestry or farming occupations
- military or humanitarian operations in endemic areas.

The indication for immunisation is stronger the longer the period of risk. We would generally consider that at-risk periods of less than 1 week would not warrant immunisation; periods of more than 1 month generally would, but the intensity of likely exposure should also be considered.

Immunisation for travellers should be performed using an accelerated schedule and should be commenced either in Australia, if time allows, or soon after arrival in Europe, if possible prior to potential exposure.

In addition, travellers should avoid unpasteurised dairy products, and protect themselves against ticks and other biting insects by protective clothing, use of

DEET-containing insect repellent, and permethrin impregnation of clothing. Travellers should inspect themselves (or each other), particularly their arms and legs and head, on at least a daily basis while at risk. Any ticks should be removed as quickly as possible by pulling them evenly and slowly with forceps applied to the tick as close to the skin as possible (the finest widely available forceps, excellent for this purpose, accompany most Swiss army pocket knives). Large ticks (suggesting a long attachment time) in Lyme disease-endemic areas (which includes many areas endemic for TBE) are likely to warrant a single prophylactic dose of doxycycline 200 mg.

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2.16 Tuberculosis

Disease

Tuberculosis (TB) is one of the leading causes of death from infectious disease in the world. One-third of the world's population is infected with TB, and almost two-thirds of these people are in Asia. Of those infected, 90% will never become sick with TB. About 5% of those infected will develop tuberculosis in the first 2 years after infection, and the remaining 5% do so over the rest of their life.

The risk of developing active disease following infection is greatest in HIV-infected and other immunocompromised patients. It is high in those recently infected, close contacts with infectious cases, children <5 years of age, and people over the age of 60. Genetic factors also have a role.

Epidemiology

Australia has one of the lowest incidences of TB in the world (5.4 per 100 000). The global incidence is about 139:100 000, with the highest rates in Sub-Saharan Africa and parts of South-East Asia, where the incidence is >300:100 000 (Map 10).

Mycobacterium bovis infection is still present in some parts of the world. The infection is spread both by inhalation and ingestion. Travellers should be advised not to drink unpasteurised milk.

Risk to travellers and expatriates

TB is generally not a highly infectious disease and not a big risk for most travellers. It usually requires prolonged exposure to an infectious case. Only 10–30% of exposed persons become infected. The greatest risk of contracting the infection occurs in those who stay with infected relatives, and healthcare workers who are moving among the sick. The risk of infection for healthcare workers has been found to be approximately 8 per 1000 person-months of travel (1 in 8 people spending a year in an endemic country).

Those who intend to live with local residents in a highly endemic region where the prevalence and incidence of the disease are much higher than in Australia (for example, up to 60 times higher in Africa and South-East Asia) are also at some risk of contracting the infection. Reviews of tuberculosis in returned travellers and missionaries have been conducted in recent years in the Netherlands, United States, and United Kingdom. Useful information can be gleaned from the experience of US Peace Corps volunteers. The rates of documented tuberculin skin test conversion per 100 volunteer years were 0.5 for the whole African region (but >3.5 in two African countries), 0.6 for east or central Europe and the Mediterranean region, and 0.7 for the Asia–Pacific region (the rate in one Asian country was >3.5). Peace Corps volunteers were not given Bacille Calmette-Guérin (BCG) vaccine.

A study of Dutch travellers staying for 3–12 months in highly endemic countries found higher rates of 3.5 per 1000 person-months of travel for tuberculosis infection (Cobelens 2000). These were even higher at 7.9 per 1000 person-months of travel in those working in a healthcare setting. These equated to a similar risk of tourists acquiring hepatitis A or malaria in Kenya.

In a study of people of Asian origin diagnosed with TB in the United Kingdom, 20% of cases were thought to be related to visits to Asia rather than to reactivation or exposure in the United Kingdom. The conclusion drawn from these sources is in keeping with the common-sense view that long-term travellers, especially those who live in close quarters with local people or work in health care, are at a significant risk of contracting tuberculous infection.

Travellers may also acquire the infection in aircraft during travel. The CDC reported results of an investigation of six instances in which passengers or flight crew travelled on commercial aircraft with a person with infectious TB. It concluded:

- the risk for M *tuberculosis* transmission on an aircraft does not appear to be greater than in other confined spaces
- M *tuberculosis* has been transmitted from an infectious crew member to other crew members, and from a passenger to other passengers
- index cases were infectious at the time of the flight

- exposure was prolonged (for instance, duration of flight >8 hours)
- greatest risk occurred in those sitting within a few rows of the index case.

Methods of prevention

- The control measures for TB in a community are:
  - early detection and appropriate treatment of active cases
  - isolation of infectious cases
  - treatment of latent infection (preventive treatment for infected persons at risk of developing disease)
  - BCG vaccination.
- Measures for an individual to prevent TB infection include:
  - wearing of protective masks for healthcare workers exposed to infectious TB cases
  - avoidance of contact in enclosed spaces (e.g. train, homes) with persons coughing actively.
- There are two measures available to travellers to prevent TB infection developing into TB disease:
  - **BCG vaccination** may reduce the risk of disease developing in persons infected. TB is different from other vaccine-preventable diseases in this regard. This is the method favoured by most Australian doctors and by us.
  - **detection of TB infection during travel via Tuberculin skin test (TST) or TB-gamma interferon blood assay** – perform prior to departure and on return, and then manage those with evidence of infection on return (by exclusion of active disease and isoniazid preventive therapy if necessary). This method is favoured by US authorities. However with the increasing incidence of drug-resistant TB worldwide, the effectiveness of preventative therapy is reducing.

The recently introduced TB-gamma interferon blood assay (Quantiferon Gold) offers some advantages over the TST. It is more specific for the detection of infection with tuberculosis than TST in those previously vaccinated with BCG, and is more sensitive for those who are immunosuppressed. It also avoids the inconvenience of the person having to return for the skin test to be read. It does not perform appreciably better than the TST in well individuals not previously vaccinated with BCG, and its usefulness in children remains under debate.

Vaccine: BCG

BCG (Bacille Calmette-Guérin) vaccine is a suspension of live attenuated M *bovis*, derived from the strain propagated by the Institut Pasteur and first tested in humans in 1921.

Dosage and administration

- Children and adults: 0.1 mL by intradermal injection.
- Infants <12 months old: 0.05 mL by intradermal injection.

Practical issues

- A tuberculin skin test must be carried out before BCG immunisation, except in infants <6 months old who may be immunised without a prior test. However these infants should also be tested if exposure to infectious TB has taken place.

  Tuberculin testing should be done at the same time as parenteral live virus vaccines (especially MMR) or else delayed 4–6 weeks, as these vaccines may transiently suppress the response to tuberculin testing. This does not apply to live oral vaccines such as OPV, oral typhoid or oral cholera vaccines.

  The requirement of tuberculin skin testing before BCG vaccination for persons older than 6 months is the government policy in Australia, and appears in *The Australian Immunisation Handbook*. It is not strictly necessary, since the early reaction to BCG vaccine is more sensitive and specific than the Mantoux test in identifying tuberculosis (see 'Accelerated response' below).
- No BCG is necessary for those with a Mantoux reaction >5 mm.
- BCG vaccine can only be given by an accredited vaccinator. Names and addresses of accredited BCG vaccinators can be obtained from state and territory health departments.

Immune response and efficacy

Expected response following BCG vaccination

The normal local response to BCG vaccination occurs within 2–3 weeks. Induration with erythema appears, and a small papule (5–6 mm diameter) is usually present after 2 weeks. This is followed by a pustule or an ulcer with scab. Local reaction is maximum in 4–6 weeks. In the great majority resolution takes place after 3–4 months leaving a scar of 4–8 mm.

The development of pathological reactions at the site of inoculation and in the regional nodes after BCG injection is expected, and is without any ill effects unless it becomes severe and unpleasant.

Slightly enlarged regional nodes are common after BCG vaccination, but are rarely noticeable unless searched for specifically. This subclinical lymphadenitis regresses spontaneously, is of no practical importance, and should not be regarded as a complication.

Lymphadenitis may appear early (within 2 months of vaccination) or late (between 2 and 8 months following vaccination). Lymphadenitis with 'softening' does not usually appear before the third month, sometimes as late as the

sixth or seventh month, and exceptionally after 2–3 years. If the enlargement is rapid (within 2 months), spontaneous drainage is more likely to occur compared to the slowly progressive form.

Tuberculin reactivity appears at 6–10 weeks in 95% of the recipients. Erythema nodosum occurs occasionally.

Accelerated response and its significance

When tuberculin reactors or those in the pre-anergic phase of TB are vaccinated, a pronounced reaction frequently occurs at the site of vaccination. A nodule with induration forms on the first or second day (within 72 hours). Scab formation and healing may be complete by 10–15 days. The intensity of the reaction varies with the level of the anergy of the individual and the potency of the vaccine.

Efficacy

BCG vaccination does not prevent tuberculous infection. It primarily reduces the risk of death from TB meningitis and disseminated disease in young children, where it has been shown to be 80% effective. Protection probably lasts for no longer than 15 years, but the duration of protection is very poorly defined.

The protective efficacy of BCG against pulmonary tuberculosis is approximately 50%, although controlled trials have shown widely differing efficacy (ranging from 0 to 80%). The wide variation in protective efficacy demonstrated in controlled trials has been attributed to differences in vaccine strains, prevalence of local (protective) environmental mycobacteria, and host factors such as age at vaccination and nutritional status.

BCG provides protection against leprosy better than it does against TB.

Repeat BCG

Despite the practice of some countries, there is no evidence to support BCG being given more than once in a lifetime. Provided there is local 'take' of the BCG (resulting in local ulceration), we do not recommend that BCG immunisation ever be repeated.

Adverse effects

BCG vaccine has a low incidence of serious adverse reactions, and is considered to be a safe vaccine.

BCG lymphadenitis is the most common complication resulting from this vaccination. The term 'BCG lymphadenitis' is used to refer to cases where lymph nodes have become large enough to be easily palpable and a cause of concern for the parents or the patient.

Small children are more liable to lymphadenitis with softening than older children and adults. Suppurative regional lymphadenitis and other local

complications occur in 4% of infants and 0.3% of older children and young adults. Abscesses in lymph nodes do not always coincide with large local reactions. About 1% of vaccinees may need medical attention as a result of an adverse event.

BCG vaccine given during the newborn period is associated with a higher risk of lymphadenitis, and reactions are more severe when the vaccine is injected subcutaneously.

BCG may cause disseminated disease in immunocompromised hosts, and the appearance of disseminated infection may be many years after the vaccination. Generalised BCG infection is extremely rare in immunocompetent persons.

Hypertrophic scars occur in an estimated 28–33% of vaccinated persons, and keloid scars occur in approximately 2–4%. The risk of keloid formation is minimised if the injection is not given higher than the level of the insertion of the deltoid muscle into the humerus.

The incidence of osteitis varies from 0.01 per million in Japan to 300 per million in Finland.

Contraindications and precautions

The use of **BCG is contraindicated** in the following:

- individuals who have previously had TB or those with tuberculin reactions >5 mm
- individuals with impaired immunity due to HIV infection, corticosteroids or other immunosuppressive agents, congenital immunodeficiencies and malignancies
- persons with significant febrile illnesses
- persons with generalised septic skin diseases
- pregnant women.

BCG in **patients on corticosteroid therapy** may result in an excessively large BCG lesion with regional adenopathy and failure to develop tuberculin sensitivity.

Serious immunodeficiency states such as severe combined immunodeficiency and AIDS are associated with increased incidence of local as well as systemic disseminated BCG infection after vaccination. The risk of BCG-related complications appears to be increased, even in patients with asymptomatic HIV infection.

Interactions

- **Oral polio vaccine**: When BCG is given to infants, there is no need to delay oral polio vaccine, as the vaccine viruses replicate in the intestine to induce local immunity and serum antibodies.

- **Other live vaccines**: An interval of 4–6 weeks should be allowed between administration of BCG vaccine and any other live vaccine (except live oral vaccines), whichever is given first. If necessary, they may be given concurrently. No further immunisation should be given for at least 3 months in the arm used for BCG vaccination, due to the risk of regional lymphadenitis.

Recommendations for BCG for travellers

These vary between different authorities:

- **The Australian Immunisation Handbook 2008** – Vaccination is generally recommended for tuberculin-negative children under the age of 5 years who will be living for more than 3 months in countries having a tuberculosis incidence ≥100 per 100 000 population. Consideration should be given to vaccination of tuberculin-negative children under 16 years of age who may be living for long periods in these high-risk countries.
- **Australian Red Cross** – Vaccination is generally recommended for all Mantoux negative delegates aged <50 years without prior BCG.
- **CDC (US) 2012** – BCG is not recommended for travellers. However, it suggest BCG may offer some protection for people who are likely to be exposed to resistant TB (MDR or XDR-TB) patients in settings where the TB infection-control measures recommended in the United States are not fully implemented.
- **WHO 2011** – 'In countries where the prevalence and incidence of TB are high, BCG vaccination should be given to infants as soon after birth as possible, and in any case, within the first year of life.' For travellers, BCG is only recommended for vaccinated infants travelling from an area of low incidence to high incidence.
- **Canada (NACI 2006)** – recommends BCG for travellers planning extended stays in areas of high TB prevalence where a program of serial tuberculin skin testing and appropriate chemotherapy is not possible or where drug resistance to prophylactic regimens is high.

One's view on the value of BCG vaccine is frequently coloured by concerns that interpretation of tuberculin reactions is difficult in BCG vaccinees. Those who oppose BCG vaccine use the tuberculin reaction to diagnose the presence of tuberculous infection and are usually strong advocates of isoniazid preventive therapy for tuberculin reactors. If one is not a strong proponent of giving isoniazid preventive therapy for all tuberculin reactors <35 years of age, the need to retain the tuberculin skin test (an imperfect test) as a diagnostic tool is not such an important issue. Also, the availability of the TB gamma interferon blood assay (QuantiFERON-TB GOLD) has removed much of the difficulty of interpreting the tuberculin reaction in BCG-vaccinated persons.

In areas where multidrug resistant TB is prevalent, the protection provided by BCG, albeit incomplete, would be welcome indeed.

Our recommendations

We recommend BCG for:

- tuberculin-negative children under the age of 5 years who will be living in developing countries for more than 3 months, but we sometimes use it for shorter durations (e.g. ≥6 weeks).
- tuberculin-negative individuals under the age of 35 years who will be living for long periods, >6 months, in high-risk countries (defined as having an incidence ≥100 per 100 000 population), in particular healthcare workers working in countries with multidrug resistant *M tuberculosis*.

The principle is: the younger the person, the longer the stay, the higher the likely TB exposure, the stronger the case for BCG.

The alternative to BCG vaccination is screening with the tuberculin skin test or TB gamma interferon blood assay, and treatment of latent infection if present (for patients with latent *M tuberculosis* infection, isoniazid given for nine months can reduce the risk of progression to active disease by up to 90%). We generally do not favour this method of protection for travellers. Interpretation of the tuberculin reaction may be difficult, and treatment of latent infection with isoniazid is not without problems and is best managed by doctors experienced in TB management.

Role of chest X-ray as a screening test

Persons commencing work in countries with high prevalence of TB are often requested to have a chest X-ray before and after their term of employment. However, chest X-rays have an extremely low yield in detecting TB in asymptomatic persons and are not recommended.

Migrants to Australia, and those applying for residency, are required to have a chest X-ray. The purpose of this procedure is to detect asymptomatic pulmonary TB in people from high-risk countries, who may benefit from early treatment.

Summary

- TB is uncommon in travellers, but transmissibility of *M tuberculosis* is variable and all travellers and expatriates are at risk.
- Tuberculous infection cannot be prevented by BCG.
- The aim is to reduce the likelihood of developing disease after infection in persons at risk.
- The risk of disease in the young can be reduced with BCG before infection has occurred; the effect of BCG is less certain in adults.

- Isoniazid preventive therapy can be given for those recently infected, to reduce the risk of subsequent disease if the infection does not involve drug-resistant organisms.

Key readings

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2.17 Typhoid

Disease

Typhoid fever is caused by *Salmonella enterica* serotype Typhi (previously known as *Samonella typhi*), which differs from most other *Salmonella* species in that it infects only humans. Typhoid is a severe systemic illness characterised by high fever, headache, malaise, anorexia, abdominal pain, non-productive cough, and constipation (more often than diarrhoea). Mild and atypical forms of the disease frequently occur. It is usually transmitted by food and drink contaminated with faecal material from a patient with typhoid fever or from an asymptomatic carrier of *S enterica* Typhi. Paratyphoid fever is a similar illness caused by *S enterica* Paratyphi A, B or C. For simplicty we will use the designations *S* Typhi and *S* Paratyphi.

The fatality rate is about 10% in untreated cases, and <1% in those given appropriate antibiotic therapy. The risk of severe illness is increased in persons with diminished gastric acid due to gastrectomy or treatment with antacids or acid-suppressive drugs, and in immunocompromised persons, for example, AIDS patients and chemotherapy recipients.

Chronic carriage, which is defined as persistence of organisms in stool or urine for more than one year, develops in 2–5% of cases even after treatment. Except in the context of antibiotic resistance, chronic carriage occurs less frequently following therapy with fluoroquinolone antibiotics than after treatment with other drugs.

The frequency of chronic carriage is higher in older individuals and in people with gallstones, which can act as a persistent nidus of infection. Long-term carriers should not be involved in food preparation.

Emerging resistance of *S* Typhi to a variety of antibiotics including chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole and quinolone antibiotics can complicate treatment, and is most prevalent in South-East Asia.

Epidemiology

In endemic areas, typhoid has been considered primarily a disease of persons 5–19 years of age; cases in children <5 years of age have been thought to account for fewer than 5% of the total number, and typhoid fever in children <2 years is infrequently reported. In these areas, attack rates usually decline with age in adults. However, recent prospective population-based studies systematically collecting blood cultures in febrile children in a number of Asian countries demonstrate typhoid is much more common in children 1–4 years old than previously recognised, with similar rates in pre-school and school-age children. Disease in infants is often mild or atypical, and thus often not recognised. In endemic areas in general, contaminated water is the most frequent source of infection, with generally small numbers of ingested organisms producing many mild and subclinical infections for each full-blown case.

In 2004, WHO estimated the global burden of typhoid to be 21 million cases annually, causing 216 000–600 000 deaths per year, predominantly in Asian children. There is a high prevalence throughout Asia, with the exception of Japan and Singapore, where infection is uncommon. High incidence of typhoid is defined as more than 100 cases per 100 000 population per year. It is highly endemic in India, Pakistan, Bangladesh, Sri Lanka, Indonesia and Papua New Guinea, with rates close to 1 per 1000 per annum documented; and moderately prevalent in Malaysia, South Korea and Mongolia. Typhoid is highly prevalent throughout the African continent and the Middle East, with the exception of Kuwait, Bahrain and South Africa. Prevalence is also high in Latin American countries, except Argentina, Brazil, Honduras, Mexico, Paraguay and Venezuela, where it is moderately endemic. In endemic regions, typhoid typically accounts for more than 75% of cases of enteric fever, and paratyphoid for the rest – an additional estimated 6 million cases worldwide annually.

Foreign travel accounts for an increasing proportion of typhoid cases seen in industrialised countries. However, the risk to travellers overall is low, about 3 per 100 000 for travellers staying 4 weeks in countries where typhoid is endemic. However the risk is highest (30 per 100 000 per month), 6 to 30 times higher than in any other region, in South Asia.

In Australia, 105 cases were reported in 2008 (NNDSS 2010), of which 92% were acquired overseas. The highest rates were in young adults and children. Half (49%) of all cases had travelled to India, and another 9% each to Bangladesh, Indonesia and Pakistan. Preliminary data for 2009 include 116 cases notified <www.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi35-nndss2009-prelim.htm>.

For travellers to areas where sanitation is likely to be poor, immunisation is useful but is not a substitute for careful selection and handling of food and water, and good hygiene and food precautions are also important for prevention of the many other enteric infections. Typhoid immunisation does not afford complete protection, particularly if heavily contaminated foods are ingested.

Vaccines

Available vaccines

- Vi polysaccharide vaccine – Typhim Vi (Sanofi Pasteur) and Typherix (GlaxoSmithKline)
- Live attenuated *S* Typhi Ty21a oral vaccine – Vivotif Oral (Berna Biotech/CSL Biotherapies).

Vi polysaccharide vaccines are also produced for local use in China, India, Vietnam, Russia and Cuba. The old whole-cell injectable heat-killed typhoid vaccine is no longer available in Australia, and production is likely to cease globally in the very near future. Both the newer vaccines are far less reactogenic and safer.

No prospective, randomised trials comparing the different vaccines have been performed. For methodological reasons, efficacy studies of the Vi and Ty21a vaccines have not been performed in areas with low typhoid incidence. However, each vaccine has been shown to provide protective efficacy of approximately 60–80% in settings where previous exposure and natural boosting are common. These data may not be directly applicable to travellers from low-incidence areas, but in the absence of evidence to the contrary, it is reasonable to assume that they can be applied.

Vi polysaccharide typhoid vaccine

Both Typhim Vi (Sanofi Pasteur) and Typherix (GlaxoSmithKline) consist of 25 µg of purified Vi capsular polysaccharide plus 0.5% phenol as preservative. They have equivalent immunogenicity and will be considered together. The combined hepatitis A–typhoid (Vi) vaccine (Vivaxim, Sanofi Pasteur) is discussed in detail in section 2.4, Hepatitis A. The typhoid component of this combined vaccine is identical to Typhim Vi. A similar HA-Vi vaccine (Hepatyrix, GSK) is currently licensed only in Europe, and is not expected to become available in Australia.

Dosage and administration

- **Dose**: children and adults 0.5 mL.
- **Administration**: IM injection

The vaccine contains purified Vi capsular polysaccharide of *S*Typhi (Ty2 strain).

Immune response and efficacy

Antibody seroconversion is observed in >90% of recipients 28 days after a single dose. Antibodies appear after about 7–15 days and reach peak values about 28–35 days after injection. As with other unconjugated polysaccharide vaccines, children <2 years of age have a weaker immune response and antibody is short-lived. The antibody response is poorer in those with pre-existing antibody, and repeat doses result in antibody levels similar to those seen after primary immunisation – a booster effect is absent.

In disease-endemic areas the serologic response to vaccine correlates with protective efficacy. However, the protective efficacy of the vaccine has not been formally studied in travellers, and it is uncertain to what extent efficacy for travellers can be extrapolated from efficacy of vaccines in endemic countries where individuals may already have some baseline immunity due to previous infection, and where natural boosters occur.

The efficacy of Vi vaccine has been evaluated in trials in Nepal (Acharya 1987), South Africa (Klugman 1987) and China (Yang 2001). In Nepal, efficacy of 72% was demonstrated over 17 months of follow-up in subjects aged from preschool to adults. In South African schoolchildren efficacy was 64% over 21 months and 55% over 3 years.

A further large efficacy trial of a Chinese-produced Vi vaccine in Guangxi, predominantly among children aged 5–19 years, demonstrated efficacy of 69% against blood culture-confirmed typhoid.

Individuals with an impaired immune system, such as those with an immunosuppressing disease or receiving immunosuppressive drugs, may not develop the expected antibody response.

Vi-negative *S* Typhi

Some strains of *S* Typhi lack Vi antigen. These Vi-negative strains are less virulent than Vi-positive strains, but nevertheless can cause disease. Anti-Vi antibody resulting from the Vi capsular polysaccharide vaccine does not ensure protection against these Vi-negative strains, which have been reported from many parts of the world. Concern has been expressed that widespread use of Vi vaccine may select for such strains. However, thus far there is no convincing evidence of emergence of Vi-negative strains and the prevalence of these remains low.

Repeat doses

The antigen in the vaccine is T-cell independent, and a true booster effect of repeat immunisation does not occur. There is minor variation in the recommended interval for repeat doses for those at continuing risk – 2 years (US: CDC 2012), 3 years (NHMRC 2008), and 2–3 years (WHO 2011). We think 3 years is reasonable given the South African trial showed protection in the third year post immunisation was well maintained, and an outbreak investigation among French soldiers in Côte d'Ivoire demonstrated twofold higher risk of

typhoid for soldiers immunised with Vi vaccine more than 3 years previously (Michel 2005).

Adverse effects

Both Vi vaccines cause fewer and milder local, and very few systemic, adverse events compared with the older heat-killed whole-cell preparation: 21–60% pain, 1% fever, 8% erythema, 2% induration.

One published comparative study (not double-blind) in Belgian adults comparing Typherix with Typhim Vi found that local redness, soreness and swelling were reported significantly more often in the 100 Typhim Vi recipients (21%, 33%, 17% respectively) than in the 300 Typherix recipients (3%, 8%, 2% respectively) (Lebacq 2001).

Contraindications and precautions

- **Age**: The Vi vaccine is not recommended for children <2 years old (NHMRC 2008, CDC 2012, WHO 2011).
- **Immunodeficiency**: The Vi vaccine is safe (but may be less effective) for immunocompromised individuals, including those with HIV.
- **Pregnancy**: The immunogenicity, protective efficacy and safety of this vaccine have not been thoroughly studied in pregnant women. Being an inactivated vaccine with few side-effects, it is not contraindicated.

The only contraindications are anaphylaxis following a previous dose of a typhoid vaccine, or from any vaccine component.

Interactions

There are no significant interactions known. Evaluation of co-administration with IPV, YF, HA, HB, rabies, D, T, Pa, 4vMenPV and MMR has shown no interference.

Live attenuated *S* Typhi oral vaccine Ty2la— Vivotif Oral

The Ty21a vaccine (Berna Biotech/CSL) is prepared from a non-pathogenic strain of S Typhi and presented as enteric-coated capsules.

Dosage and administration

- **Dose**: four doses, one each on days 1, 3, 5 and 7, 1 hour before food is preferable to the standard three-dose course (four doses give better and longer protection than three doses, estimated to be 40% more effective).
- **Administration**: The vaccine should be swallowed whole and not chewed, as stomach acid may kill the vaccine organisms. It is recommended that it be taken with cool liquid (no warmer than 37°C). It should be refrigerated, but not frozen, until taken.

Travellers frequently leave oral typhoid vaccine capsules sitting at room temperature. Vaccine potency declines but is maintained above the minimum potency requirements upon exposure to 20–25°C for up to 7 days; even when stored at 30–33°C potency, is maintained for at least 5 days, and for at least 12 hours when stored at 37°C.

It is essential to go through the instructions with the traveller. Non-compliance with one or more of these instructions (particularly completion of all doses) occurs in approximately 30% of travellers and reduces protective efficacy (Stubi 2000). Variable compliance, the time required to complete the course, potential interference with antibacterial and antimalarial medication, and a lower recommended age limit of 6 years are the major disadvantages of the oral vaccine.

Immune response and efficacy

The protective efficacy of the vaccine is estimated to be approximately 50–80%. The highest efficacy shown was 96% in an initial 3-year study of Egyptian children aged 6–7 years given three doses of liquid vaccine immediately following a dose of antacid. Seroconversion is optimal by 14 days after a third dose and 7 days after a fourth dose. Completion of the course at least 1 week prior to potential exposure is ideal.

By practical necessity, all studies on vaccine efficacy have been performed in areas endemic for typhoid, where partial immunity from natural infection may also provide some protection. The efficacy of vaccination with Ty21a among travellers has not been comprehensively studied. Vaccine failures in travellers have been described, but this is not unexpected.

A liquid formulation of the vaccine has been shown to be more effective than capsules. Though licensed in a number of countries, a liquid formulation is unfortunately not currently being produced and we are not aware of any plans to resume production.

Efficacy of different regimens

Major WHO-sponsored field trials of the Ty21a vaccine have been carried out in Indonesia (one trial) and Chile (four trials involving over half a million schoolchildren). Two or three doses have inferior efficacy and/or durability than four doses.

The main findings can be summarised (Levine 2008):

1. Two enteric-coated capsule doses given 1 week apart provide moderate protection (52–71%) for 2 years, but negligible thereafter.

2. Unlike almost every other vaccine, longer dosing intervals are less effective. Weekly and 3-weekly dosing regimens are less effective than alternate day dosing, e.g. three doses given at 21-day intervals are less efficacious (49%) than when given on alternate days (67%).

3. A comparison of two, three and four doses of enteric-coated capsules in a randomised trial in Santiago, Chile, with over 55 000 children in each group, after 3 years of follow-up showed the following incidence rates: 184.6, 160.5 and 95.8 per 100 000 vaccinees (the four-dose result being highly statistically significantly different from the other two) (Ferreccio 1989). This is the basis for the US, Canadian and our recommendation for four vaccine doses rather than three.

It is interesting to note that in Chile two or three doses of enteric-coated capsules showed 42% and 56% efficacy, respectively, against paratyphoid B.

Myron Levine in *Vaccines*, 5th edn, recommends that if more than 3 weeks have passed since the last dose of an incomplete course, the course should be restarted. NHMRC, WHO and CDC do not make a recommendation on this. Given the evidence about poorer protection for doses spaced 1 and 3 weeks apart compared with those given on alternate days, we think Levine's recommendation is reasonable (if often impractical).

Boosters

Recommendations regarding booster interval for Ty21a vaccine vary around the world, from 1 to 7 years. In Chilean schoolchildren, three doses of enteric-coated capsules provided 67% protection over 3 years and 62% protection over 7 years (Levine 1999). (Three doses of a liquid formulation provided even better protection: 77% for 3 years and 78% protection over 5 years.)

NHMRC (2008) recommends that the primary course be repeated 3 years after a three-dose course and 5 years after a four-dose course (the latter like CDC 2012). We prefer a four-dose course and recommend this be repeated after 5 years.

Adverse effects

Side-effects are infrequent and not significantly different from placebo recipients in clinical trials, even among children 1–5 years of age, although abdominal pain, nausea, vomiting, diarrhoea, rash, fatigue and myalgia have been reported.

Contraindications and precautions

- **Age**: The enteric-coated capsule formulation is not licensed for children <6 years in Australia or elsewhere. (In contrast, the liquid formulation previously available in a number of countries can be used in children 2 years and above.)
- **Immunodeficiency**: Because the Ty21a vaccine is a live bacterial vaccine, it should not be given to patients with immune defects due to disease (including HIV) or drug therapy. Ty21a can be given to those with immunocompromised close contacts, as excretion of Ty21a has never been detected in any subject given the dose in the vaccine, and secondary transmission of the vaccine strain has not been demonstrated. WHO (2011) recommends that Ty21a can be given to HIV-infected asymptomatic persons as long as

their CD4 count is more than 200/mm^3. Though consistent with NHMRC (2008) and CDC (2012), we would avoid Ty21a and prefer to use the inactivated Vi vaccine in HIV-infected and other immunocompromised patients.

- **Pregnancy**: The safety of the oral typhoid vaccine in pregnancy is not known. Though there is no known basis for concern, we would favour the inactivated Vi vaccine during pregnancy.
- **Other**: It is prudent to avoid giving the vaccine during diarrhoeal or severe acute illness.

Interactions

Antibiotics: The growth of the live Ty21a strain is inhibited in vitro by various antibacterial agents. Travellers should not be on antibiotics at the time of taking Ty2la vaccine, and antibiotic treatment should if possible be separated by at least 3 days from administration of the vaccine.

Antimalarials: Recommendations about potential interactions between antimalarials and Ty21a are inconsistent and confusing. Some antimalarials, particularly mefloquine, have been shown to inhibit Ty21a in vitro. In clinical trials, giving Ty21a vaccine together with chloroquine, mefloquine, or chloroquine plus Fansidar (pyrimethamine-sulphadoxine), did not suppress the IgG O antibody response to Ty21a, whereas concurrent proguanil did. However, the significance of these findings is unclear, because, while IgG O antibody has been shown to correlate with the protection conferred by Ty21a, it is unlikely to be the mechanism of immunity.

Subsequently, a randomised, double-blind controlled trial showed that co-administration of atovaquone–proguanil (Malarone) did not reduce typhoid IgG O antibody responses. However, in this trial the first dose of Ty21a vaccine was given together with CVD 103 HgR live oral cholera vaccine. The latter vaccine is no longer available in Australia.

All authorities recommend that Ty21a should not be given together with antimicrobials active against Salmonellae, such as most antibiotics including doxycycline, and that such drugs should be given more than 3 days before or after Ty21a. However current recommendations regarding antimalarials and Ty21a vaccine differ, e.g.:

- **NHMRC** (2008) recommends Ty21a can be given with mefloquine or atovaquone-proguanil (Malarone)
- **WHO** (2011) recommends mefloquine and proguanil not be given concurrently with Ty21a
- **CDC** (2012) recommends that no antimalarials should be given concurrently with Ty21a
- the current **Australian Prescribing Information** (CSL 2010) recommends chloroquine and sulphadoxine-pyrimethamine (Fansidar) be given 12 hours

apart from the vaccine and proguanil 10 days apart, and has a confusing statement regarding concurrent mefloquine: 'A lower IgG response was observed compared to taking Vivotif Oral Typhoid Vaccine alone, however the immune response was not affected and vaccine efficacy was not compromised.' The first two statements are contradictory, and vaccine efficacy has not been measured in this context.

We recommend a cautious approach and that, with the exception of chloroquine, all antimalarials – including doxycycline, mefloquine and atovaquone-proguanil (Malarone) – should be given at least 3 days before or after Ty21a.

Other vaccines: NHMRC (2008) recommends at least 8 hours' separation between administration of inactivated oral cholera vaccine and Ty21a vaccine as the buffer in the cholera vaccine might affect the gut transit of Ty21a. There is no evidence for interference by concurrent administration of other vaccines with Ty21a, including live vaccines such as yellow fever and oral polio vaccines.

Recommendations for use of typhoid vaccines

Typhoid vaccination is not legally required for international travel. It is recommended for travellers to areas where there is a recognised risk of exposure to *S* Typhi. This includes all developing countries where the safety of the water supply and food hygiene are poor or uncertain. It is generally recommended for all South and South-East Asian, Middle Eastern, African and Latin American countries, particularly for travellers staying longer than 2–3 weeks and anyone likely to encounter settings in which sanitation and food hygiene are poor.

Travellers with decreased gastric acid due to gastrectomy, gastric atrophy, gastric acid suppressive therapy or antacid ingestion are likely to be at increased risk of disease. The vaccine is also recommended for persons who have close exposure to a known carrier of *S* Typhi, for example through household contact.

We regard the Ty21a and Vi vaccines as essentially being of equivalent, incomplete, but useful efficacy, and base the choice on practical aspects and patient factors, including contraindications, preference, vaccine availability, and cost. The Ty21a vaccine has the advantage of oral administration, and a longer interval till repeat immunisation is indicated.

The Vi vaccine may be preferable in the following situations:

- when hepatitis A immunisation is also indicated, enabling the combined hepatitis A–typhoid vaccine to be used with no extra injection required
- for imminent travel when there is insufficient time for the course of Ty21a to be completed before departure
- for children aged 2–6 years, for whom the available Ty21a capsules are not recommended

- for travellers who are or should be taking antimicrobial or antimalarial agents at the time typhoid vaccine is required
- for travellers who are immunocompromised or HIV-infected
- for pregnant women
- for persons who prefer a single, well-tolerated injection rather than a four-capsule series taken over a week
- if compliance with the refrigeration requirements and multiple-dose regimen of Ty21a is anticipated to be difficult or uncertain.

We lean towards Vi vaccine because of simplicity, lack of precautions and contraindications, and, most importantly, the knowledge that the patient has received the best available protection when they leave the clinic, rather than running an average 30% chance of non-compliance with the schedule for Ty21a.

There are no data available concerning the use of one vaccine as a booster after primary vaccination with a different vaccine, but using either Ty21a or the Vi vaccine in individuals who have been previously vaccinated with one or more different typhoid vaccines is considered effective and safe.

The available typhoid vaccines are approximately equivalent in efficacy.

Special note: children aged 1–2 years

The only typhoid vaccine approved in Australia for children aged between 1 and 2 years was the injectable whole-cell vaccine, which is no longer available or appropriate. For children aged between 1 and 2 years who will be travelling extensively or who will be living in typhoid endemic regions, we feel a good case can be made for giving the Vi vaccine.

Vi conjugate vaccines with improved immunogenicity and protection in young children will hopefully become available in the future.

Table 2.16.1 Dosage and schedule for typhoid vaccines

	Vivotif Oral – Berna/CSL	Typhim Vi – Sanofi Pasteur	Typherix – GlaxoSmithKline
Type of vaccine	Oral live attenuated Ty21a	Vi capsular polysaccharide	Vi capsular polysaccharide
Recommended age	≥6 years	≥2 years	≥2 years
Primary course	1 capsule on alternate days × 4	0.5 mL IM	0.5 mL IM
Repeat doses	4 dose course every 5–7 years	0.5 mL IM every 3 years	0.5 mL IM every 3 years

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2.18 Varicella

Background and epidemiology

Varicella-zoster virus (VZV) occurs worldwide and causes a highly contagious infection. Primary infection with VZV causes varicella (chickenpox). Following

primary infection, VZV becomes latent in the dorsal root ganglia. Reactivation of the latent virus presents as herpes zoster (shingles), occurring most often late in life. As with many other infections, varicella is more often severe and complicated at older ages and in the immunocompromised.

The incubation period is 10–21 days. Transmission occurs through contact of a susceptible person with someone with varicella or, less commonly, zoster. The period of infectivity is from 2 days before onset of rash till all the lesions are crusted (5–7 days). The secondary attack rate in susceptible household contacts of a person with varicella is 80–90%. Susceptible individuals who are exposed should be considered infectious from days 10 to 21. Those with a reliable history of varicella or zoster can be considered immune. About 60–70% of adults without a history of varicella are also immune on testing.

In Australia and other temperate areas, infection occurs most often during childhood, with about 75% of individuals having been infected by age 12 years. In tropical areas a higher proportion of cases occur in adults.

No epidemiological data on travel-related varicella are available.

Vaccines

Live attenuated VZV vaccines have been available in Australia since 2000, and from November 2005 a single dose has been funded under the NIP for all children at 18 months of age, with a catch-up dose funded for children from 10 to <14 years of age.

Two vaccines are available in Australia. Both are lyophilised preparations of a live attenuated strain of VZV.

- **Varilrix** (GlaxoSmithKline) contains $\leq 10^{3.3}$ plaque-forming units; human serum albumin; lactose; neomycin; polyalcohols.
- **Varivax Refrigerated** (CSL/Merck) contains ≤1350 plaque-forming units; sucrose; gelatin; urea; monosodium glutamate; residual components of MRC-5 cells; trace amounts of neomycin and foetal bovine serum from MRC-5 culture media.

A combination vaccine containing measles, mumps, rubella and varicella vaccines (MMRV) will be available in Australia in the near future.

A zoster vaccine is registered in Australia. This is formulated from the same VZV strain as Varivax, but has a much higher viral titre.

Dosage and administration

- Dose: 0.5 mL (requires reconstitution) administered SC
  - one dose in children from 12 months to <14 years of age
  - two doses at least 1–2 months apart in ≥14 years of age.

- Can be given concurrently with any other vaccines, using separate syringes and injection sites.
- If not given simultaneously with other live viral parenteral vaccines (e.g. MMR), should be given at least 4 weeks apart.

Consideration is being given to introducing a two-dose varicella vaccine schedule for all children.

Recommendations

VZV vaccine should be offered to:

- anyone ≥14 years who is non-immune (determined by serology undertaken in those with a negative history for varicella and/or zoster), particularly:
  - high risk occupations such as healthcare workers, teachers and child-care workers
  - women prior to pregnancy
  - parents of young children
  - household contacts of immunosuppressed persons.
- susceptible persons within 3–5 days of exposure.

Although there is no specific recommendation for travellers, the pre-travel consultation provides a useful opportunity to offer VZV vaccine.

Immune response and efficacy

Seroconversion occurs in 90–100% of immunised children. The response to a single dose decreases progressively with age. For adults, about 80% develop antibodies after one dose and 99% after a second dose. Cell-mediated immune responses are also elicited. Recent evidence suggests that immunity does not persist as long as was first thought. A second dose in children is optimal to provide an immune response more like natural infection, reducing the risk of vaccine failure and increasing population immunity.

The efficacy of one dose in children is approximately 85% against any disease and >95% against severe varicella, and higher if two doses are given. There is an increased risk of vaccine failure in those receiving vaccine before 15 months of age.

Varicella vaccine is effective if given within 3–5 days after exposure, and can therefore be of use in controlling outbreaks.

Combination MMRV vaccines produce similar rates of seroconversion to all four vaccine components compared with MMR and monovalent varicella vaccines administered separately, though data on the use of MMRV vaccines are not available for those >12 years of age.

Boosters

It is possible that booster doses may be recommended in future for long-term protection against varicella or zoster.

Adverse events

Adverse events are generally mild and well-tolerated, and include:

- Local reactions
  - pain, redness and/or swelling
  - 7–30% of vaccine recipients, less in children than in adults.
- Fever
  - 15% of children and 10% of adults, although similar rates occurred in those who received placebo.
- Rash
  - 3–5%.
  - usually generalised maculopapular, sometimes vesicular
  - median of five lesions
  - occurs after 5–26 days
  - most varicella-like rashes occurring in the first 2 weeks after immunisation are related to wild virus or other causes
  - rash at the injection site in 1–5% (usually maculopapular), with a median of two lesions, more common in children than adults.
- **Zoster** in vaccine recipients can rarely be caused by vaccine virus, but may also be due to previous natural varicella infection. The risk of developing HZ is currently thought to be lower after vaccination than after natural varicella virus infection, and reported cases have been mild.

Contraindications and precautions

Contraindications include anaphylaxis to any vaccine component, impaired immunity, and pregnancy.

Immunisation should be deferred in the setting of moderate or severe acute illness.

Pregnancy

Although there are no reports of congenital varicella or other adverse fetal outcomes following immunisation shortly before or during pregnancy, pregnancy should be avoided for 1 month after immunisation.

Children

The vaccine is approved from 9 months of age, and recommended by the NHMRC from 12 months.

Immunocompromised hosts

Varicella vaccine is unique among prophylactic vaccines, particularly live attenuated vaccines, in having been evaluated early and extensively in immunocompromised hosts, particularly leukaemic children, over a period of close to 30 years. In fact the vaccine development was initially largely directed towards this group. Although adverse events occur more frequently following immunisation of immunocompromised hosts, the vaccine has been shown to be protective and free of serious adverse events in these patients. This provides an unusually high level of reassurance regarding the safety and efficacy of the vaccine.

There is an increased risk of vaccine failure in children taking oral steroids. No increase in adverse events has been observed following immunisation of HIV seropositive subjects.

Asymptomatic or mildly symptomatic HIV-infected children with CD4 cell percentage ≥25% should be immunised.

Contact with immunocompromised persons

Transmission of vaccine virus to contacts of vaccinated individuals is rare. In the United States, only six cases of transmission of vaccine virus have been documented with 56 million doses distributed between 1995 and 2005. All cases were mild and all were associated with rash in the vaccinee. Thus vaccinees, including healthcare workers and those who have household contact with an immunocompromised person, only need avoid contact with that person if they develop a rash within 6 weeks of immunisation, for the duration of the rash. Immunisation is not contraindicated in those in contact with young infants or pregnant women.

Blood products

Immunisation should, if possible, be delayed for 3 months after receipt of a blood product containing VZV-antibody (for example, immunoglobulin, blood transfusion), and if possible administration of such a blood product should be delayed 3 weeks or more after immunisation.

Aspirin use

Although aspirin use at the time of wild varicella is associated with a risk of Reye's syndrome, no adverse events associated with aspirin have been reported following immunisation.

Varicella vaccine and tuberculin skin test

Any effect of varicella vaccine on tuberculin testing is unknown. However, because measles (and possibly mumps and rubella) vaccine can suppress the

response to PPD, it seems prudent to recommend that, as for measles-containing vaccine, PPD testing should be done before or at the same time as varicella immunisation, or else delayed by 4–6 weeks.

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2.19 Yellow fever

Disease

Yellow fever is a serious viral haemorrhagic fever that is spread by mosquitoes. The clinical illness follows a short incubation period of 2–5 days and is characterised by fever, jaundice and bleeding. The case fatality rate without supportive treatment is greater than 60% in non-immune adults. A vaccine that offers a high level of protection against yellow fever is available and is effective in preventing infection in travellers and individuals living in endemic countries.

Epidemiology

Yellow fever exists in two endemic areas: across central Africa, and the northern part of South America. It has three types of transmission cycle:

- jungle (sylvatic) cycle – an enzootic viral disease transmitted among non-human primate hosts by a variety of mosquito vectors, which may also bite and infect humans
- urban cycle – an epidemic disease of humans transmitted from infected to susceptible persons by the *Aedes aegypti* mosquito.

Both transmission cycles occur in Africa, while jungle transmission predominates in South America.

- An intermediate (savannah) cycle – a mode of transmission that occurs only in Africa and involves transmission of YFV from *Aedes* spp. to humans living or working in jungle border areas. In this cycle, the virus may be transmitted from monkeys to humans or from human to human via these mosquitoes.

Although *Aedes aegypti* mosquitoes are found in all warm climates, for the past 90 years yellow fever has only occurred in Africa and South America. Why the disease is not seen in other regions with warm climates (including the Middle East, South-East Asia and the Pacific) has never been explained.

There was been a dramatic increase in the number of cases of yellow fever in the late 1980s and 1990s. WHO estimates that some 200 000 cases occur each year, with almost all of these in Sub-Saharan Africa.

The risk of yellow fever for travellers is difficult to determine and to date has been based on the risk to indigenous populations. For a 2-week stay, the risks for illness and death due to yellow fever for an unvaccinated traveller to an endemic area are:

- West Africa – 50 per 100 000 and 10 per 100 000, respectively
- South America – 5 per 100 000 and 1 per 100 000, respectively.

Yellow fever vaccine (Stamaril)

The vaccine is manufactured by Sanofi Pasteur SA and distributed in Australia by Sanofi Pasteur. It consists of a heat-stable, lyophilised live attenuated virus (17D-204 strain) that is grown in chicken embryos. Each 0.5 mL dose contains not less than 1000 mouse LD 50 units. The vaccine should be stored in the refrigerator at 2–8°C and not frozen.

Dosage and administration

- **Dose:** 0.5 mL by IM or SC injection.
- **Booster dose:** one 0.5 mL dose every 10 years.

The vaccine is reconstituted by injecting syringe contents (diluent) into an ampoule of freeze-dried vaccine. After complete dissolution, the vaccine is drawn back into the syringe and is ready to be injected. Once reconstituted the vaccine can be kept at room temperature, but should be protected from light and used within 1 hour.

Immune response and efficacy

The vaccine induces neutralising antibodies in 90% of vaccine recipients within 10 days after inoculation, and in 99% within 30 days. Immunity is

durable, and probably close to lifelong, although revaccination is recommended at 10-year intervals.

Simultaneous administration of other vaccines and immunoglobulin

The administration of MMR, varicella and smallpox should be concurrent with yellow fever vaccine. If this cannot be achieved, they should be given 4 weeks apart. However, if time is limited, the vaccines should be given within whatever time is available. Sabin (OPV) can be given at any time. Heat-killed parenteral cholera vaccine, now outdated, should be given 3 weeks apart from yellow fever vaccine; either can be given first.

Immunoglobulin does not affect the immune response to yellow fever vaccine and may be given concomitantly.

The antibody response to yellow fever vaccine is not inhibited by simultaneous immunisation with:

- BCG
- cholera – oral
- measles
- diphtheria-pertussis-tetanus
- meningococcal vaccine
- poliomyelitis – OPV and IPV
- hepatitis A
- hepatitis B
- tetanus
- typhoid vaccine – oral and parenteral.

There are no data on possible interference between yellow fever and plague, rabies or Japanese encephalitis vaccines.

Side effects

- **Mild**: 2–5% of vaccinees have mild headache, myalgia, low-grade fever or other minor symptoms 5–10 days after vaccination (most commonly on the sixth or seventh day). Daily activities may be curtailed in up to 1% of vaccinees.
- **Severe hypersensitivity**: Anaphylaxis is reported to occur at a rate of 1.8 cases per 100 000 doses of yellow fever vaccine administered.
- **Yellow fever vaccine-associated neurotropic disease**: A total of 50 cases of YF vaccine-associated neurotropic disease have been documented. Histori-

cally, these occurred in infants 7 months of age or younger, predominantly in infants 4 months of age or less. In more recent years, four cases of encephalitis have been reported among adults, with onset 4–28 days after immunisation, all following first doses (Monath 2008). Recovery has generally been rapid and complete. One case of fatal meningoencephalitis has been reported in an immunocompromised HIV-infected man, but prospective surveillance established in 1993 during an immunisation campaign in Kenya did not demonstrate more frequent severe reactions in HIV-infected persons.

The estimated incidence of vaccine-associated neurotropic disease ranges from four to six cases per 1 000 000 doses (in the United States) to one in 8 million.

- **Immediate hypersensitivity reactions**: These are characterised by rash, urticaria and/or asthma, are extremely uncommon (incidence <1:1 000 000), and occur principally in persons with histories of egg allergy. These individuals should be referred to an allergy clinic.
- **Yellow fever vaccine-associated viscerotropic disease**: 59 cases of severe multiple organ system failure following the administration of the yellow fever vaccine have been described since 1973 (Lindsey 2008, Monath 2010). This complication occurred predominantly in older adults and was associated with both the 17D-204 and 17DD yellow fever virus strains. Vaccine recipients generally presented within 2–5 days of vaccination with an illness characterised by fever, myalgia, and gastrointestinal symptoms, followed by a rapid progression to hypotension, liver, renal and respiratory failure, encephalopathy, lymphocytopenia, thrombocytopenia, disseminated intravascular coagulation, and death in the majority. The illness is similar to fulminant yellow fever caused by wild-type yellow fever virus, and the reported case-fatality ratio for YEL-AVD is 65%. Vaccine-type virus has been isolated in some cases. For two cases, including a fatal Australian case, their intended travel did not include the YF endemic zone.

  Crude estimates of the reported frequency of this vaccine-associated illness range from 0.9 to 2.5 per 1 000 000 doses distributed. The risk is highest in individuals over the age of 60–65 years. In those over the age of 75, the risk is 12 times higher than in young adults. This syndrome has not been reported in individuals receiving booster doses of the vaccine; vaccine viraemia is not detectable in those receiving booster doses. The syndrome is probably caused by unusual susceptibility of the individual host. Four (17%) of the 23 vaccinees reported with this syndrome had a history of thymus disease (thymectomy and thymic tumour), suggesting that thymic dysfunction is an independent risk factor.

Contraindications and precautions

Age

Infants **<6 months** of age are more susceptible to serious adverse reactions (for example, encephalitis) than older children and **should never be immunised**.

The NHMRC 2008 recommends the vaccine for persons from **9 months of age** travelling or living in yellow fever infected areas. The requirement for entry into Australia applies only to travellers >1 year old.

The CDC 2012 Yellow Book (Gershman 2012) recommends the vaccine be given to children **≥9 months** of age, if travelling or living in areas of South America and Africa where yellow fever is officially reported, or to countries that require yellow fever immunisation.

For adults aged 60 years and over, yellow fever vaccine should be given with a precaution. Compared to younger people, in individuals aged ≥60 years there is an increased risk for serious adverse events after vaccination. The rate of any serious adverse event in people aged ≥60 years is 8.3 per 100 000 doses, compared with 4.7 per 100 000 for all vaccine recipients. The risk of both YEL-AND and YEL-AVD is also increased in this age group (1.8 and 1.4 per 100 000 doses respectively, compared with 0.8 and 0.4 per 100 000 for all vaccine recipients). Both YEL-AND and YEL-AVD are seen almost exclusively in primary vaccine recipients, and therefore a greater level of caution should be exercised with older travellers who may be receiving yellow fever vaccine for the first time. If travel is unavoidable, the decision to vaccinate travellers aged ≥60 years needs to weigh the risks and benefits of the vaccination in the context of their destination-specific risk for exposure to YFV (Gershman 2012).

Because of the risk of serious adverse events including vaccine-associated viscerotropic and neurotropic disease that can occur after yellow fever vaccination, only people who (1) are at risk of exposure to YFV or (2) require proof of vaccination to enter a country should be vaccinated.

Pregnancy

Safety of yellow fever vaccine during pregnancy has not been established, and the vaccine is contraindicated on theoretical grounds. Congenital infection appears to occur at a low rate (probably 1–2%), and has not been associated with fetal abnormalities. Pregnant women inadvertently vaccinated should be reassured that there is no risk to themselves and very low (if any) risk to the fetus. They should be followed to determine the outcome of the pregnancy.

Avoid vaccination while pregnant unless travel to high-risk areas is unavoidable.

Nursing mothers

Whether the vaccine virus is excreted in human milk is unknown. Two YEL-AND cases have been reported in exclusively breastfed infants whose mothers were vaccinated with yellow fever vaccine. The CDC recommends as a precautionary measure that vaccination of nursing mothers should be avoided because of the potential risk for transmission of the vaccine virus to the breastfed infant. However, nursing mothers travelling to a yellow fever–endemic area should be vaccinated.

Thymic disorder or dysfunction

In view of the four reported cases of yellow fever vaccine-associated viscerotropic disease in persons with thymic disorder, travellers, irrespective of age, with a history of thymic disorder or dysfunction – including myasthenia gravis, thymoma, thymectomy, or DiGeorge syndrome – should not be given this vaccine. If travel to a yellow fever–endemic area cannot be avoided in these individuals, a medical waiver should be provided, and counselling on protective measures against mosquito bites should be emphasised.

Altered immune states

On theoretical grounds the vaccine is contraindicated in persons with immunodeficiency due to cancer, HIV/AIDS, transplantation or treatment with immunosuppressive drugs, since prolonged viraemia may increase the risk of encephalitis.

Persons with asymptomatic HIV infection may be vaccinated if exposure to yellow fever cannot be avoided and the individual's CD4 count is over 200×10^9 cells/L. If travel to a yellow fever–endemic area cannot be avoided in these individuals or in those with symptomatic HIV, a medical waiver should be provided, and counselling on protective measures against mosquito bites should be emphasised.

Hypersensitivity to eggs

Yellow fever vaccine should not be given to those with known anaphylactic hypersensitivity to chicken eggs (manifested as urticaria, swelling of the mouth and throat, difficulty breathing or hypotension).

If immunisation is considered important because of a high risk of exposure for an individual with a questionable history of egg hypersensitivity, an intradermal test dose may be administered under close medical supervision, with adrenaline and resuscitation expertise and equipment on hand. In our view, such procedures should be undertaken in a hospital setting. Test doses are absolutely contraindicated for those with anaphylactic egg allergy (NHMRC 2008).

In one large study in military personnel, only 16% of egg-sensitive subjects developed any reaction on intradermal testing, and all these were mild. Intradermal skin testing had a moderately high negative predictive value (0.80), but a lower positive predictive value (0.57) for an allergic reaction.

An intradermal test dose involves 0.1 mL of vaccine. In the absence of a local reaction, such as an urticarial wheal, or a general reaction after 10–15 minutes, the remaining 0.4 mL can be given IM or SC. In the case of a positive intradermal test (wheal of ≥5 mm) and there is a strong need for protection, desensitisation with increasing SC doses at 15–20 minute intervals could be conducted by experienced personnel.

If international travel regulations are the only reason to vaccinate a traveller in whom any of the above contraindications apply, efforts should be made to obtain a waiver. A physician's letter clearly stating the contraindication to vaccination has been acceptable to some governments.

Inactivated yellow fever vaccine

The concerns over yellow fever vaccine-associated neurotropic and viscerotropic disease have led to the development of an inactivated yellow fever vaccine. The vaccine is derived from the XRX-001 purified whole-yellow fever 17D virus produced in Vero cell cultures that has been inactivated with β-propiolactone and adsorbed to aluminum hydroxide (alum) adjuvant. The safety and immunogenicity of the vaccine was recently tested in a double-blind, placebo-controlled, dose-escalation, phase 1 study of 60 healthy subjects aged between 18 and 49 years of age; the recipients received two doses of vaccine 21 days apart. Neutralising antibodies developed in 100% of subjects who received two doses of 4.8 μg of antigen compared with 88% of subjects who received 0.48 μg of antigen in each injection. The vaccine was well tolerated with only a single case of urticaria in the high-dose arm (Monath 2011). The durability of neutralising antibody response is not yet known; however the promising initial results with this vaccine have paved the way for the initiation of a double-blind phase 2 clinical study.

Recommendations

There are two reasons for giving this vaccine: protection, and legal requirement.

For protection

For people living or travelling in endemic areas, the vaccine is recommended for those aged ≥9 months who are:

- living or travelling in areas of **active transmission** (i.e. infected areas)
- **travelling outside urban areas in countries within yellow fever endemic zones** (see maps 11, 12).

Actual areas of yellow fever virus activity far exceed the endemic zones officially reported. In recent years, fatal cases of yellow fever have occurred in unvaccinated tourists visiting rural areas within the yellow fever endemic zone. Many countries regard endemic areas as infected areas. Check the WHO book (International Health and Travel 2011), CDC Yellow Book (Health Information for International Travel 2012) or website for the official requirements of the countries to be visited. Information concerning known or probable infected areas is also available from WHO <www.who.int>.

The 2012 CDC recommendations are based on 4 categories of risk for YFV transmission that apply to all geographic areas: endemic, transitional, low potential for exposure, and no risk. Yellow fever vaccination is recommended for travel to endemic and transitional areas. Vaccination is generally not recommended for travel to areas with low potential for exposure, although vaccination should be considered for a small subset of travellers whose itinerary could place them at increased risk for exposure to YFV. Based on the revised CDC criteria for yellow fever risk classification, the CDC yellow fever maps and country-specific information now designate 3 levels of yellow fever vaccine recommendations: recommended, generally not recommended, and not recommended. Countries that contain areas with low potential for exposure to YFV are not included on the official WHO list of countries with risk of YFV transmission. Proof of yellow fever vaccination should therefore not be required if travelling from a country with low potential for exposure to YFV to a country with a vaccination entry requirement unless that country requires proof of yellow fever vaccination from all arriving travellers.

Travellers to coastal Brazil or Peru, Cuzco and Machu Picchu do not need vaccination. It is generally not recommended for coastal Ecuador or Columbia and no longer required for travel to Quito or Bogotá (Gershman 2012). For these destinations a waiver letter that is stamped with an official yellow fever licence number should be provided.

Until the recent appearance of reports of vaccine-associated viscerotropic and neurotropic disease, the vaccine was generally regarded as innocuous. Although the frequency of serious adverse events is low, the vaccine should clearly only be given when medically justified, particularly in the elderly.

The incidence of vaccine-associated viscerotropic disease (estimated to be 1:400 000) is high enough to restrict the use of the vaccine to those who are truly at risk. The risks of illness and death due to yellow fever for an unvaccinated traveller are estimated to be 1:1000 per month and 1:5000 per month respectively, during a non-epidemic period. The risk of infection may increase to 1:15 per month during an epidemic. In West Africa the most dangerous time of the year is during the late rainy and early dry seasons (July to October). All rural areas present a risk.

'The risk of wild-type yellow fever exceeds the risk of vaccination for persons travelling to rural areas in the zone of endemicity, to inland towns and cities, or to urban areas sustaining yellow fever outbreaks.' (Monath & Cetron 2002). Vaccination should clearly be given to all travellers in these situations.

Give yellow fever vaccine for any rural travel within the endemic zone, even if not legally required.

For legal requirement

The vaccine is recommended for those overseas travellers who:

- visit **nations that require a certificate of vaccination** from all travellers who enter the country, even if those persons are only in transit in the country (a certificate may also be required by some countries outside yellow fever endemic zones for persons who have travelled through endemic zones)
- visit yellow fever infected countries and proceed to countries with an immunisation requirement.

Australian requirements

A valid international yellow fever vaccination certificate is required from travellers >1 year of age entering Australia within 6 days of having stayed overnight or longer in an infected country, as listed by WHO (International Health and Travel 2011). For those not visiting endemic areas, this requirement goes beyond medical indications.

International requirements

India has strict yellow fever vaccination requirement for travellers arriving in India from 'infected' countries (except infants up to the age of 6 months). A list of countries deemed to be infected, according to India, appears in the WHO International Travel and Health (2011). Where a case of yellow fever is reported from any country, that country is regarded by the Indian government as infected with yellow fever and is added to this list.

Malaysia and Singapore are frequent stopover places for travellers, and both regard yellow fever endemic zones as infected areas. Age exemption for these two countries is ≤1 year old.

Yellow fever vaccine certificate

The vaccination certificate is only valid if:

- the vaccine has been approved by WHO
- the vaccine has been administered at an approved yellow fever vaccination centre designated by the Commonwealth Department of Health & Ageing and recorded with WHO
- the certificate conforms with the following
  - it is printed in English and French
  - it is completed in English or French
  - it is signed by a person authorised by the Commonwealth Department of Health & Ageing

- the date is recorded in day-month-year sequence, with the month written in letters (e.g. 3 September 2011)
- the official stamp, issued by state and territory health departments, on behalf of the Commonwealth Department of Health & Ageing, is affixed to the certificate by the medical practitioner in charge of the vaccination centre or, in his/her absence, by his/her deputy
- the certificate must include the traveller's name and signature.

An international certificate of vaccination against yellow fever is valid for 10 years, beginning 10 days after vaccination (i.e. the vaccination is not valid unless it is given 10 days before entry into an at-risk country).

Countries that require proof of yellow fever vaccination from all arriving travellers

Angola	Gabon
Benin	Ghana
Burkina Faso	Guinea-Bissau
Burundi	Liberia
Cameroon	Mali
Central African Republic	Niger
Congo, Republic of the	Rwanda
Côte d'Ivoire	São Tomé and Príncipe
Democratic Republic of the Congo	Sierra Leone
French Guiana	Togo

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Chapter 3

Malaria Prevention

Chapter outline

3.1 Introduction

Malaria is one of the 10 most prevalent and deadly diseases in the world. Each year, 300–500 million clinical cases occur, and an estimated 1.5–2.7 million people die from the disease. Malaria is found in over 100 countries (Map 13), but more than 90% of all malaria cases are in Sub-Saharan Africa, and most of the deaths are in young children in remote rural areas of Africa. However, the mortality of falciparum malaria in most industrialised countries remains 1–5%.

Malaria is the most common cause of fever in returned travellers. Approximately 50–100 million international travellers from non-tropical regions visit countries where malaria is endemic annually, with ~30 000 cases of travel-associated malaria acquired.

In Australia, malaria is almost always a disease of travellers. There are rare reports of local transmission, for example, an individual living near an airport, recent cases in the Daintree region and in residents of islands north of Australia. More than 600 000 Australians annually travel to areas where malaria is endemic, and 600–800 cases of imported malaria are reported in Australia each year. It has been estimated that approximately 1.5:1000 Australian travellers develop malaria.

Plasmodium falciparum accounts for one-half of all cases of imported malaria in the northern hemisphere, with 85% acquired in Africa. In contrast, vivax malaria is more frequently diagnosed than falciparum malaria in Australian travellers returning from surrounding malarious areas in the Asia–Pacific

Plasmodium knowlesi

A new form of malaria is being reported in recent years. This is the monkey malaria, caused by *Plasmodium knowlesi*; it is the fifth major human malaria parasite. *P knowlesi* is normally a parasite of long-tailed macaques. This parasite is mostly found in South-East Asian countries, particularly in Borneo, Malaysia, Myanmar, Philippines, Singapore, Thailand and neighbouring countries. In 1965, the first case of a natural infection of knowlesi malaria in humans was reported in a traveller who had returned from visiting peninsular Malaysia. Since 2004, there have been increasing reports of the incidence of *P knowlesi* infections among humans in South-East Asia. Humans who work at the forest fringe or enter the rainforest to work are at risk of infection. Increasing deforestation in South-East Asia is bringing many more macaques into close and direct contact with humans. Hence more and more people who live in the semi-urban areas are being found to be infected with knowlesi malaria. A fifth of the cases of malaria diagnosed in Sarawak, Malaysian Borneo are due to *P knowlesi*. *Plasmodium knowlesi* is less prevalent in Africa.

Plasmodium knowlesi parasite replicates and completes its blood-stage cycle in 24 hour cycles, resulting in fairly high loads of parasite densities in a very short period of time. It may cause severe malaria. It does not produce hypnozoites in its exoerythrocytic stage, and does not cause relapsing malaria as does *P vivax* and *P ovale*.

Under the microscope, the early parasite stages of *P knowlesi* look very similar to *P falciparum*, the most severe form of human malaria, while the later parasite stages are indistinguishable from the more benign *P malariae*. Existing antimalarial therapy, such as chloroquine and mefloquine, is effective.

region. In Australian returned travellers with malaria, *P vivax* accounts for approximately 75% of reported cases (Elliott 2004). Severe and fatal malaria associated with severe anaemia and respiratory complications have recently been reported with *P vivax*.

The subject of chemoprophylaxis for malaria appears difficult because:

- travellers differ in the amount of time spent in endemic areas and in their likelihood of exposure through different activities, and may change their itineraries
- the risk in each country varies with the region and the season (for example, Bangkok has no risk, yet the Thai border region is high-risk); therefore, one cannot prescribe prophylaxis simply according to country to be visited
- resistance to chemoprophylactic drugs increases year by year and no drug is completely safe and effective
- recommendations on malaria prevention by various government and other authorities differ, and vary from year to year
- even travel medicine doctors have different opinions on the optimal regimen.

The important message is: there is no infallible malaria chemoprophylaxis, and practitioners must spend some time during the consultation educating travellers about symptoms and preventive measures.

Authorities differ in their recommendations. Travellers going overseas, particularly if they are going on a safari in Kenya, are likely to meet people on different regimens. It would be wise to warn them of this possibility. At the time of publication, no official body exists in Australia to update recommendations on malaria chemoprophylaxis. Therapeutic Guidelines Antibiotic contains a section on malaria prophylaxis, and is the closest we have to an 'official' recommendation.

Advice given to the traveller should be:

- uniform
- accurate
- simple
- understandable.

3.2 Preventive measures

Prevention of malaria and its complications is achieved through four measures:

- awareness of risks
- early diagnosis and treatment
- minimising exposure to mosquitoes
- prophylactic drugs.

Awareness of risks

The first measure is education of travellers. Travellers should be advised of the risk of malaria in areas to be visited, and recognise the importance of the preventive measures.

Table 3.2.1 shows the varying risks of the four main types of malaria according to geographic region.

An approximate relative risk (RR) of *P falciparum* malaria acquisition (by region) was determined using GeoSentinel data, with areas visited as numerators and World Travel Organization (WTO) data as estimates for denominators (Table 3.2.2). The highest risk areas are Sub-Saharan Africa, the Solomon Islands and Papua New Guinea. The risk is low in the common tourist spots of Thailand, Malaysia and Indonesia.

Although travel to Oceania is associated with a high relative risk of malaria, the majority of travellers returning from Papua New Guinea with malaria are

Table 3.2.1 Varying risk for malaria according to geographic region

Region	*P falciparum*	*P vivax*	*P malariae*	*P ovale*
Africa	High	Low (except North-east Africa)	Low	Moderate (West)
South-East Asia	Low to moderate	Moderate	Low	Low (Philippines, Indonesia)
South Pacific	Very high	Moderate to high	Low	Low (PNG)
India, South Asia	Low to moderate	Moderate	Rare	None
South America	Low to moderate	Moderate	Low	None
Central America	Low	Low to moderate	Rare	None
Caribbean*	None to low	None to low	Rare	None
Middle East	Rare	Low	Rare	None

* Malaria occurs only in Haiti and the Dominican Republic
Source: Keystone 2001

infected with *P vivax*. In fact, compared to other malaria endemic regions of the world, travellers to Papua New Guinea are ten times more likely to be infected with *P vivax* than *P falciparum* malaria (Elliott 2004). The risk of contracting malaria in those who spend long periods in malarious areas is much higher than in short-term tourists. However, short durations of exposure in areas of endemicity are sufficient for malaria acquisition; the GeoSentinel study (Leder 2004) found that 5% of malaria infections occurred after a trip with a duration of ≤1 week. Although 90% of returned travellers with *P falciparum* infections presented within one month of return, approximately 40% presented either during

Table 3.2.2 Relative risk of malaria among travellers, 2000 through 2002[a]

Region visited	Relative risk (95% CI)
Very low risk area[a]	1.0
Caribbean	3.8 (1.9–7.5)
North Africa	6.9 (3.6–13.3)
South America	8.3 (4.9–13.9)
South-East Asia	11.5 (8.3–15.9)
Central America	37.8 (24.0–59.6)
South Asia	53.8 (37.4–77.4)
Oceania	76.7 (50.8–115.9)
Sub-Saharan Africa	207.6 (164.7–261.8)

a Non-risk/very low-risk areas were Europe, North-east Asia, Australia/New Zealand, North America, and the Middle East.
Source: Leder 2004

their travel or within the first week of return. Travellers should be warned that malaria may occur as early as one week after entering a malarious area.

Malaria is a local disease. Even in countries where the overall risk is relatively low, there may be foci of high transmission (for example, in Kenya the risk of malaria is high near Lake Victoria and low in the game parks). The risk is generally higher in rural areas than in the cities, and in the wet/monsoonal seasons than in the dry.

Any fever occurring while away or after return from a malarious area, irrespective of prophylaxis taken, may be due to malaria.

Early diagnosis and treatment

As few people can completely escape mosquito bites during travel, and no chemoprophylactic drugs are completely effective, travellers will continue to contract malaria. Most deaths from malaria are due to delayed presentation to a doctor, or to a doctor's failure to suspect or recognise the disease.

Early diagnosis and treatment is the key to preventing death and severe disease. There is nothing specific about the clinical illness of malaria. Malaria is a great mimic; it may resemble influenza, gastroenteritis, pneumonia, hepatitis or meningitis.

The essential element in the diagnosis of malaria is to consider it. You should remind travellers of the following:

- Any fever occurring while away or after return from a malarious area, irrespective of prophylaxis taken, may be due to malaria. (Falciparum malaria usually occurs within 3 months of return, but may present later, particularly in travellers who have taken an incomplete course of chemoprophylactic drugs.)
- If fever occurs they should consult a doctor promptly, tell the doctor where they have been, voice their suspicion of malaria, and ask for a blood film to be taken.
- They should do so within 48 hours of onset of fever, and earlier if they are more than moderately unwell.

This advice is even more important for young children, pregnant women, and asplenic individuals, in whom the infection is more severe and rapidly progressive.

Travellers who are likely to be >24 hours away from medical help should be given one or more treatment courses of an antimalarial drug (see section 3.4, Standby emergency self-treatment).

Minimising exposure to mosquitoes

Stringent measures to prevent mosquito contact reduce the risk of contracting malaria ten-fold. These measures are the mainstay of malaria prevention and include:

- well-screened or sealed accommodation, or the use of mosquito nets, preferably impregnated with permethrin (the use of impregnated bed nets can reduce the risk of malaria by 50%)
- protective clothing, covering arms and legs in the evenings
- avoidance of outside activities between dusk and dawn
- use of mosquito repellents on bare skin, especially on ankles and feet
- wearing light-coloured clothing; dark clothing attracts mosquitoes, as do strong scents
- use of an insecticide aerosol in the room to kill mosquitoes before retiring
- use of mosquito coils or vaporising mat containing a pyrethroid.

N,N-diethylmetatoluamide (DEET)

The most effective mosquito repellents contain DEET (for example, 'Rid' and 'Aerogard Tropical Strength'). Roll-on preparations are cheaper than sprays, which may be more pleasant to use in hot, humid climates. Protection provided by DEET is proportional to the dose. Duration of protection is 1 to 3 hours for 20% DEET, up to 6 hours for 30% and up to 12 hours for 50%. There is no further increase in duration of protection beyond a concentration of 50%. When both sunscreen and DEET are required, DEET should be applied second. DEET reduces the efficacy of sunblock, however sunscreens do not reduce the effectiveness of DEET. Untreated travellers in proximity to treated ones are more apt to be bitten.

Encephalopathy in children has followed repeated and extensive application of lotions with as low as 20% DEET. However, concerns about the neurotoxicity of DEET in children are generally misplaced. The rare cases of toxic encephalopathy occurred mostly in the setting of long-term, heavy, frequent or whole body applications. The American Academy of Pediatrics (2003) recommends the maximum concentration of DEET be 30%. DEET is not recommended for use on infants under 2 months of age. Products with a concentration of up to 30% are safe for use in children when used according to the directions on the product label.

DEET should not be applied near the eyes or on the part of the hands likely to have contact with the mouth or eyes. It should be applied only to intact skin that is exposed (not under clothing). It should be washed off on returning to a protected environment.

All DEET-containing repellent should be kept well away from plastics, including watch straps, cameras, plastic jewellery and spectacle frames, as it may dissolve or damage them.

Repellents not containing DEET are less effective. For the few individuals who develop a rash with DEET, the best alternative is dimethyl phthalate.

Picaridin

Picaridin is a new mosquito repellent similar in effectiveness to DEET. It is not available in Australia, but is obtainable in many countries overseas. CDC is recommending it as an alternative to DEET compounds.

Unlike DEET, picaridin is odourless, not greasy, less likely to irritate skin, and does not damage plastic or fabrics. The drawback is that protection is short for formulations with low concentration of picaridin (2 hours for concentrations below 9%), and reapplication every 2–3 hours is necessary.

Permethrin

Permethrin is safe, colourless, odourless and biodegradable (and, unlike DDT, does not persist in the environment). It is a contact insecticide and not an insect repellent, as it does not release a repelling vapour; insects may still bite the user on exposed parts of the body.

Permethrin is effective against a wide range of insects, including mosquitoes, fleas, bedbugs, head and body lice, ticks and scabies. It adheres well to fabric, especially pure cotton, and will survive 5–10 washes in hot or cold water, and lasts for up to 6 months.

The best way to utilise permethrin is to impregnate mosquito nets, youth hostel sheets or T-shirts with it. It is not recommended for skin application.

Permethrin-impregnated bed nets have been shown to significantly reduce malaria and all-cause mortality in children in Africa, and have become the mainstay of malaria-control programs in many countries. The safety of permethrin is attested by its availability as the initial topical treatment of choice for scabies.

Permethrin-treated clothing used in combination with DEET-based repellents can provide excellent protection against mosquito bites.

3.3 Prophylactic drugs

General considerations

Purpose of chemoprophylaxis

Chemoprophylaxis aims at preventing death and severe disease, and not at preventing all malaria infections (i.e. it is targeted primarily at travellers who are at risk of *Plasmodium falciparum* infection).

Table 3.3.1 Efficacy of antimalarial chemoprophylaxis in Peace Corps volunteers

Drug	Person-months	Infections	Incidence	Risk ratio
Cq	843	26	3.1	1.00
Cq + Pg	1775	36	2.0	0.66
Mq bi-weekly	3268	45	1.4	0.45
Mq weekly	1122	4	0.4	0.12

Cq = chloroquine weekly, Pg = proguanil daily, Mq = mefloquine
Source: Lobel 1993.

No drug can provide complete protection, and travellers may develop malaria despite perfect compliance. However, prior antimalarial prophylaxis has been found to reduce the severity of imported falciparum malaria (Lewis 1992). Chemoprophylaxis also significantly reduces fatality rates among non-immune malaria patients (Krause 2006).

Table 3.3.1 above shows the incidence (cases per person-months) of US Peace Corps volunteers who spent 2 years abroad working in West Africa between October 1989 and February 1991.

Timing of prophylaxis

If a drug is to be an effective suppressant it must reach a steady-state concentration by the time the parasites enter the blood (6–10 days after first exposure to infection). The drug should be continued long enough after exposure ceases to ensure that a high proportion of malaria parasites, which may be developing in the liver, have emerged into the blood where they will be inactivated by the drug. For drugs that act on the blood stage, the most common recommended compromise between the ideal and the practical is 4 weeks after leaving a malarious area. A shorter period suffices for drugs that act on the pre-erythrocytic stage. (See individual drug for the recommended duration.)

Side-effects of prophylactic drugs

Approximately 20–40% of travellers will get some side-effects from these drugs. Most are mild, but up to 10% of travellers on any prophylactic regimen get adverse effects severe enough to interfere with daily activities. Very few are disabled to the degree of going to bed, and the incidence of these side-effects tends to decrease with time. It is essential to tell travellers about drug side-effects; however, it is equally important not to frighten them to the stage that they do not take prophylaxis. Advise them that 1:4000 travellers to a high-risk area with chloroquine resistance will die from malaria if no prophylaxis or only chloroquine is taken.

Cost

Atovaquone–proguanil (Malarone) is expensive, and cost is a consideration for the majority of those who travel for more than 2 weeks.

Importance of compliance

Emphasise the importance of compliance to your travellers, as studies have identified a two- to four-fold increased risk of malaria because of noncompliance with prescribed prophylaxis.

Non-adherence rate among travellers varies between 30% and 70%. The usual reasons given are confusing and conflicting information, perceived or actual side-effects of the drug, and problems with multiple medications.

Travellers taking a daily as opposed to a weekly regimen, those staying more than 1 month in a malarious area, and young adults travelling on their own are less likely to be compliant with their chemoprophylaxis regimen. Antimalarial advice should be stressed for these at-risk individuals.

Need to make a choice

No drug is completely safe or effective; therefore, the decision to use a preventive drug and the choice of drug must weigh up the risk of malaria and the risk of side-effects. The choice is an individual one. It is often difficult to know how to advise travellers who visit low-risk areas. It may be justified not prescribing chemoprophylaxis for travellers going to areas where the risk of malarial infection is very low so as not to subject them to the risk of side-effects of the medication (see examples in Appendix 1, Common travel destinations).

Drugs

Doxycycline

Dose

- **Adult**: 100 mg (1 tablet)/day, starting 1–2 days before entering malarious areas and ceasing 4 weeks after leaving these areas.
- **Children >8 years**: 2 mg/kg up to 100 mg daily starting 1–2 days before entering malarious areas and ceasing 4 weeks after leaving these areas. Contraindicated below the age of 8 years.

Actions and indications

Doxycycline is effective against the blood stage of *P falciparum* and *P vivax*. It is as effective as mefloquine. It has some activity against the pre-erythrocytic (liver) stage of these parasites, but not sufficient for it to be used as causal prophylaxis. There is no known resistance.

The half-life of doxycycline is 16–18 hours. Phenytoin, carbamazepine and barbiturates shorten this to approximately 7 hours. Because of its short half-life its

use needs to begin only 1–2 days before entering a malarious area. Food does not interfere with its absorption.

Doxycycline can be used in areas with chloroquine-resistant *P falciparum*. It is an alternative to mefloquine and malarone for short-term travellers, and is particularly useful for people with epilepsy or histories of psychiatric illness visiting areas of chloroquine-resistant malaria in East and West Africa and in Oceania. It also provides the added usefulness of prophylaxis against leptospirosis and rickettsial infections.

The safety of long-term use of doxycycline has not been clearly established. Doxycycline 50 mg per day has been used for many years as treatment for acne, with very few reported serious problems and no reported deaths related to its use. There is no convincing data suggesting that doxycycline should not be used for long-term prophylaxis.

Side-effects

Vaginal thrush: The risk of candidal infections is increased and thus women should carry antifungal therapy for self-treatment.

Gastrointestinal: Nausea or vomiting occur in approximately 4%, most frequently if taken on an empty stomach. Oesophageal irritation, pain and ulceration can occur if the tablet sticks in the oesophagus. Therefore swallow the tablet while upright with an adequate quantity of water, preferably not immediately before retiring.

Photosensitivity reaction: The exaggerated sunburn reaction may be minimised by avoiding sunlight (visible light is as important as UV light in this phototoxicity reaction), using sunscreen and taking the drug in the evening. Onycholysis (loosening of the nails) and discolouration of the nails rarely occur.

Pregnancy and young children: Doxycycline should not be used in pregnancy or in children <8 years of age (<12 years according to the British guidelines). WHO recommends that pregnancy should be avoided for approximately 1 week after stopping the drug.

Oral contraceptive pill: Although tetracyclines and other antibiotics have been cited as a cause of oral contraceptive failure, a recent case-control analysis failed to demonstrate any significant association. However, travellers should be warned that failure may occur rarely, particularly if doxycycline causes vomiting close to taking the oral contraceptive pill and breakthrough bleeding indicates inadequate hormone levels. In this situation alternative methods of contraception should be used.

Concurrent use of doxycycline with carbamazapine, phenytoin or barbiturates may result in decreased doxycycline serum concentration due to induction of microsomal enzyme activity, thereby resulting in a 50% reduction of the

half-life of doxycycline. Adjustment of doxycycline dosage may be necessary with either a twice daily dosing schedule (100 mg bid) or 200 mg daily.

Anticoagulant therapy: Concurrent administration of doxycyline and anticoagulants have caused altered haematologic and coagulant parameters and bleeding. In reported cases the anticoagulant abnormalities usually developed within 7–10 days after starting doxycycline (Baciewicz 2001).

Practical tips

When prescribing doxycycline one should advise travellers to:

- take it with food
- avoid prolonged and direct sun exposure
- use a sunscreen that absorbs UV radiation
- carry an anti-thrush preparation (for females, those with a history of candidiasis, and/or those planning to take doxycycline for an extended period) – single dose clotrimazole pessaries are usually most convenient
- take it regularly. Compliance with daily doxycycline is poorer than with weekly mefloquine. Traveller preference is a factor here. Travellers taking other daily medications may find a daily drug easier; others prefer a weekly drug.

Mefloquine

Dose

- **Adult**: 250 mg base (1 tablet) weekly starting 1–3 weeks (see Practical tips page 172) before entering malarious areas and ceasing 4 weeks after leaving these areas.
- **Children**: 5 mg/kg base.

Actions and indications

Mefloquine is effective against the blood stage of all species of *Plasmodium*. It is highly effective as treatment and prophylaxis against both vivax and falciparum malaria. But, as with all other antimalarials, emergence of resistance of *P falciparum* to this drug has occurred following its use. Resistance to mefloquine has been confirmed on the borders of Thailand with Burma (Myanmar) and Cambodia, in the western provinces of Cambodia, and in the eastern states of Burma (Myanmar) (see Map 14).

Peak blood levels occur 11–48 hours after administration, and food increases the bioavailability of mefloquine.

The half-life of the drug is 6–33 days (mean 21 days). It takes 6–7 weeks for mefloquine to get to a steady-state level of approximately 600 ng/mL. A loading

dose of 250 mg daily for 3 days will allow this therapeutic level to be reached in 4 days (Boudreau 1993). Rapidly achieving levels of >620 ng/mL, which correlates with a prophylactic efficacy of 95%, may benefit persons entering an area of high intensity chloroquine-resistant *P falciparum* exposure.

Mefloquine is a recommended option for use in travellers who are visiting countries with documented chloroquine and anti-folate combination resistance, and who are considered to be at risk of contracting malaria. There has been no increase in adverse effects with long-term use.

Side-effects

Gastrointestinal: Side-effects such as nausea, vomiting, and loose stools tend to be mild, transient and self-limited, and occur in approximately 20% of users. Severe oesophageal symptoms (burning, 'throat constriction', sensation of something stuck) and oesophageal ulceration may occur if mefloquine is not swallowed with an adequate amount of fluid.

Neurological:

- **Serious neuropsychiatric** events such as psychosis, encephalopathy and convulsions are rare. One should not consider mefloquine alone in this issue. Mefloquine and chloroquine are both quinoline derivatives, and the quinolines produce CNS effects. Doxycycline and malarone do not cause neuropsychiatric side-effects.

  In a study of >140 000 European travellers to Africa, the incidence of serious neuropsychiatric adverse effects (1:10 000) was found to be no higher with mefloquine than with chloroquine when given as prophylaxis, and on par with that in the general population (Lobel 1993).

  If mefloquine is given in a treatment dose the incidence is much higher, between 1 and 3% (1:200 in Caucasians and 1:1200 in Asians).

- **Milder neuropsychological symptoms** such as dizziness, headache, confusion, mental clouding, anxiety, agitation, vivid dreams or nightmares, insomnia, mood changes, ataxia and depression occur in about 5–10%. They are sometimes disabling and distressing. The boundary between the very unpleasant and truly psychotic reactions is difficult to delineate. These 'neuropsychological' side-effects occur especially when mefloquine is given as treatment, and may also occur when the drug is used as prophylaxis. They usually occur early in its use; 40% of these events associated with prophylactic doses have occurred after the first dose and 75% by the third dose. If side-effects have not occurred in the first month they are unlikely to develop. The incidence is not age-dependent, but there is a predominance of female patients among those with side-effects.

Mild reactions pass off if the drug is withheld. Travellers should discontinue mefloquine if they notice unexplained anxiety, depression, restlessness or confusion.

Opinions differ on the frequency of these less serious, but potentially disabling, neuropsychological reactions. Swiss and American experts believe neuropsychiatric adverse effects are no more frequent among mefloquine takers than among those who take chloroquine plus proguanil. Other European and the British experts do not share this view.

Precautions and contraindications

Pregnancy is not a contraindication to the use of mefloquine and it is safe in the second and third trimesters, but the issue of the first trimester is unresolved. A study of 500 pregnant women given mefloquine from 2 weeks before conception for the first 3 months of pregnancy showed no increase in the incidence of congenital anomalies (2%, compared to a background rate of 2–3%). In more than 1000 women who inadvertently took mefloquine during early pregnancy reported to the manufacturer, no increased risk of any obstetric/fetal problems was noted. Thus, its use as prophylaxis during pregnancy in high-risk situations is justified. Women on mefloquine should take reliable contraceptive precautions for the duration of prophylaxis and for 2 months (CDC) or 3 months (WHO) after the last dose.

Use in children:

- Mefloquine is not approved in Australia for use in children weighing <45 kg.
- CDC 2010 has no lower age or weight limit.
- WHO 2010 does not recommend it for infants weighing <5 kg.

We are not aware of any reports of neuropsychiatric effects of mefloquine in children, and children generally tolerate mefloquine better than adults. We are happy to use mefloquine for a child weighing >5 kg, with appropriate indication.

A practical difficulty is accurately breaking a tablet in quarters. We suggest that, where a tablet is required, a tablet cutter be used. This simple, inexpensive device can be purchased from a pharmacy.

Children generally tolerate mefloquine better than adults; we are happy to use it down to 3 months of age or 5 kg in weight.

Effect on coordination and spatial discrimination: The incidence of dizziness is higher among mefloquine users than with other prophylactic drugs (>5% of those given mefloquine prophylactically). This is transient and dose-related, and the symptom resolves within 72 hours. Persons involved in tasks requiring fine coordination and spatial discrimination (e.g. air crews, scuba divers,

mountaineers) should generally not use mefloquine for prophylaxis, and avoid such tasks for a period of time following therapeutic use. However, many military forces allow pilots and those handling weapons to take mefloquine, rather than risk malaria. Also, detailed studies of hundreds of subjects involving rigorous testing of neuropsychological function, coordination, spatial judgement and fine motor skills, as well as flight performance, show no differences between those on and not on prophylactic mefloquine.

Effect of alcohol: A controlled study demonstrated that the combination of mefloquine and alcohol, at least at low blood-alcohol concentrations, has no negative impact. However, there are case reports where binge drinking appeared to have precipitated severe psychiatric reactions in combination with mefloquine prophylaxis (Wittes 1995).

We recommend that travellers not drink alcohol on the day and the day after taking mefloquine.

Patients on cardiac drugs: Mefloquine has occasionally been associated with asymptomatic sinus bradycardia and a prolonged QT interval, and the makers recommend it should not be used by those receiving beta-blockers, calcium-channel antagonists, or other drugs that may prolong or alter cardiac conduction. However, many hundreds of travellers have taken mefloquine while on beta-blockers without any adverse effects. The consensus is that mefloquine may be used concurrently with beta-blockers or calcium-channel blockers if there is no underlying arrhythmia. It is best not to use mefloquine for persons with cardiac conduction abnormalities (Richter 1997).

Patients with diabetes: Mefloquine should be used with caution by diabetic patients. Hypoglycaemia has occurred under special circumstances (Assan 1995). Recent work in Australia shows that normal subjects commonly experience a reduction of over 0.5 mM in blood glucose with mefloquine use. This may explain some mefloquine side-effects and the occasional adverse interaction with alcohol.

Patients requiring treatment for malaria: Due to its long elimination half-life, caution is required in using mefloquine to treat malaria in persons who have been taking mefloquine prophylaxis or who may have had a therapeutic dose of mefloquine in the previous 1–2 weeks.

In addition, quinine, the quinolines and mefloquine are similar as regards pharmacology and cardiovascular and neurological toxicity. Therefore, they should not be used concurrently, and if they are used sequentially, drug administration must be carried out with extreme caution and under close clinical monitoring.

Mefloquine can be used 12 hours after the last dose of quinine because quinine has a short half-life.

Practical tips

The following measures, not all of which have been subjected to controlled trials, may be adopted to **minimise adverse effects of mefloquine**:

- Take mefloquine in the evening with or after food.
- Drink a full glass of fluid in a sitting or standing position with the medication, and maintain adequate hydration throughout the trip.
- Avoid alcohol on the day of taking mefloquine and the day after.
- If adverse symptoms occur with high blood levels (i.e. on the first and second day after taking mefloquine), split the 250 mg tablet and take half twice a week. Compliance may be a problem with this method.
- If sufficient time is available before leaving, start mefloquine 3–4 weeks before departure. This allows enough time to identify a substantial proportion of travellers who will not be able to tolerate mefloquine, to arrange an alternative, and for symptoms to subside if disabling side-effects occur.

The **contraindications** for mefloquine are:

- persons with a history of seizures
- persons with other neurological and/or psychiatric disorders or a history of such disorders
- travellers with cardiac conduction abnormalities or hypersensitivity to the drug.

It should be used with caution by:

- women in the first trimester of pregnancy
- children <5 kg in weight (WHO 2010)
- travellers involved in tasks requiring fine coordination and spatial discrimination, and scuba divers.

Despite all the concerns about mefloquine, the vast majority of travellers on mefloquine prophylaxis have tolerated the drug and only approximately 5% have had to change to an alternative regimen.

Atovaquone–proguanil (Malarone)

Dose

- **Adult**: 1 tablet per day, starting 1–2 days before entering malarious areas and ceasing 7 days after leaving these areas.* Each tablet contains atovaquone 250 mg and proguanil 100 mg. The daily dose should be taken at the same time each day with food or milk.

- **Children**: See section 7.2, Children).

* If a traveller is taking mefloquine or doxycycline as prophylaxis and needs to change the medication (because of side-effects) to atovaquone–proguanil before a full course has been completed during or after travel, the standard duration of prophylaxis for atovaquone–proguanil may be insufficient. The atovaquone–proguanil should be continued for 4 weeks after the drug change or 1 week after returning, whichever is longer, but not beyond 4 weeks after return. This is because the drugs have different modes of action that affect the parasites at different stages of the life cycle.

Actions and indications

Atovaquone–proguanil has activity against both the blood and pre-exoerythrocytic (liver) stages of *Plasmodium* spp. Because of this activity against the liver stage, and provided the medication is commenced before entering an endemic area, atovaquone–proguanil can be stopped only 1 week after leaving a malarious area. It has no effect on the hypnozoites of *P vivax*.

Half-life of blood level is 2–3 days for atovaquone and 17 hours for proguanil. Atovaquone–proguanil must be taken daily.

Atovaquone–proguanil is highly effective in preventing malaria in both semi-immune residents and in non-immune travellers. Protective efficacy against falciparum malaria is about 95%, and a little lower against vivax malaria. Atovaquone–proguanil is thus a further option for prevention of malaria when travelling to areas with chloroquine-resistant *P falciparum*.

It may be particularly useful for travellers:

- who undergo short or repeated trips to high-risk chloroquine-resistant areas
- who, for various reasons, cannot take mefloquine or doxycycline.

Atovaquone–proguanil is more expensive than mefloquine or doxycycline, but the reduced period of prophylaxis (7 days after leaving a malarious area) means that for short visits to malarious areas (≤2 weeks) the cost may be acceptable to most travellers (see Table 3.3.3).

Side-effects

Side-effects are uncommon. The most frequent are diarrhoea, abdominal pain, nausea, vomiting, headache, and mouth ulcers. None is likely to be sufficiently severe to require ceasing the medication. There has been one case report of icteric hepatitis associated with the use of malarone; however abnormalities of serum liver enzymes are usually mild and self-limiting. It is better tolerated than mefloquine, doxycycline or chloroquine–proguanil.

Precautions and contraindications

Pregnancy: Insufficient data on the use of atovaquone–proguanil during pregnancy precludes its use in pregnancy at present.

Lactation: Not recommended.

Use in children: See section 7.2, Children.

Use in patients with medical problems: No dose-adjustment of atovaquone–proguanil is necessary in elderly persons or travellers with mild-to-moderate hepatic insufficiency. However, travellers with severe renal insufficiency should not use atovaquone–proguanil.

Drug interactions

- oral typhoid vaccine: An interval of 10 days after completion of oral typhoid vaccine series is recommended before beginning atovaquone–proguanil.
- Concurrent use of **tetracycline**, **metoclopropamide (Maxalon)**, **rifampicin** or **rifabutin** and atovaquone–proguanil is not recommended because of a reduction in plasma concentration of atovaquone.
- Atovaquone increases the AUC (area under the curve) of zidovudine and etoposide; thus caution should be exercised during concomitant administration.

Contraindications

Atovaquone–proguanil is contraindicated in those who have known hypersensitivity to either atovaquone or proguanil. One case of anaphylaxis has been documented in a patient receiving atovaquone–proguanil for treatment of uncomplicated falciparum malaria. The drug is also contraindicated in individuals with severe renal impairment (CrCl <30 mL/min).

Chloroquine/hydroxychloroquine

Chloroquine is no longer obtainable in Australia; hydroxychloroquine (paludrine) has taken its place. The action, dose in base, adverse effects and usage are the same for both drugs.

Dose

- **Adult**: 300 mg base (2 tablets) per week, starting 1 week before entering malarious areas and ceasing 4 weeks after leaving these areas.
- **Children**: 5 mg/kg base once/week, up to a maximum of 300 mg base/week (see chapter 7.2).

Actions and indications

Chloroquine is effective against the blood stage of *P vivax*, *P ovale* and *P malariae*. The resistance of *P falciparum* to chloroquine has been confirmed in all

areas with falciparum malaria except the Dominican Republic, Haiti, Central America west of the former Panama Canal Zone, Egypt, and some countries in the Middle East. Due to this widespread chloroquine resistance, chloroquine alone has very little role to play in the prevention of falciparum malaria. Chloroquine-resistant *P vivax* is now present in Papua New Guinea, Solomon Islands, West Papua, Vanuatu, Burma (Myanmar) and Guyana.

Steady state can be achieved rapidly with a weekly regimen of 5 mg of base per kg body weight (300 mg for adults of normal weight) if the first dose is repeated on the second day of prophylaxis. However, for convenience, chloroquine is usually commenced 1 week before departure.

Side-effects

Gastrointestinal: Minor gastrointestinal disturbances occur frequently. If these cause discomfort, they can be lessened by taking the drug with food, or taking half the dose on 2 occasions each week.

Neuropsychological: Like mefloquine, chloroquine is a quinoline derivative and can cause minor neuropsychological adverse effects such as headache and dizziness. Chloroquine-induced psychosis occurs more frequently than has been generally recognised (see page 169 under Neurological side-effects of mefloquine).

Pruritus in dark-skinned individuals is common (chloroquine binds to melanin).

Precautions and contraindications

Pregnancy and young children: Chloroquine is safe and well tolerated at the recommended dose. It has a narrow safety margin and overdose in children can be fatal.

Psoriasis: Chloroquine should be avoided if there is a history of generalised psoriasis. Exacerbation of psoriasis usually occurs 2–4 weeks after starting the drug, whether given either as antimalarial treatment or as prophylaxis. It usually improves rapidly on withdrawing the drug and initiating topical treatment. Its frequency varies between series and is unrelated to the dose or preceding state of psoriasis. Several other chloroquine-like drugs, including primaquine, quinidine and proguanil, can cause the same reaction.

Eyes: Retinal changes are said to occur after prolonged use, and a cumulative dose of 100 g has been suggested as the maximum dose that can be taken without risk of eye damage. This applies only to patients taking chloroquine on a daily basis for rheumatological problems. At the antimalarial dose of 300 mg weekly, it would take well over 5 years to reach a total dose of 100 g. An association between a weekly chloroquine dosing regimen and drug-induced retinopathy has not been demonstrated (Lange 1994).

Liver: Chloroquine should be used with caution in alcoholics, in persons with liver disease, and in persons taking hepatotoxic drugs.

People with a history of **epilepsy** or **porphyria** should not take chloroquine.

There is an **interaction** with intradermal rabies vaccine: see section 2.13, Rabies.

Proguanil

Dose

- **Adult**: 200 mg (2 tablets) per day starting 1 day before entering malarious areas and ceasing 4 weeks after leaving malarious areas.
- **Children**: 3 mg/kg (see chapter 7.2).

Actions and indications

Proguanil acts on the blood stage and on the primary exo-erythrocytic (liver) stage of all species except for *P malariae*. Because of its action on the primary exo-erythrocytic cycle, it may be effective as a prophylactic agent against *P falciparum* when the merozoites are resistant. Its activity is on par with chloroquine, and it may be used in its place. However, strains of *P falciparum* resistant to proguanil are present in scattered foci in all endemic areas. Some strains of *P vivax* are also resistant to this drug.

Proguanil is used either alone instead of chloroquine for those who cannot take or tolerate chloroquine, for chloroquine-sensitive areas, or in combination with weekly chloroquine in chloroquine-resistant areas (see below). The combination is not as effective as either mefloquine, doxycycline or atovaquone–proguanil against falciparum malaria, and resistance developed rapidly when the drug was used on a large scale as single drug prophylaxis.

The combination of chloroquine and proguanil is moderately effective in Africa, but not in the South-East Pacific region (Papua New Guinea, the Solomons) or the Thai–Burmese border region.

The combination of chloroquine and proguanil can be considered:

- for travellers who cannot take doxycycline, mefloquine or atovaquone–proguanil, in areas with chloroquine-resistant *P falciparum*. This may include pregnant women and young children.
- for long-term travellers in areas with chloroquine-resistant *P falciparum*. Expatriates who reside in malarious areas for years often take chloroquine alone or a combination of chloroquine and proguanil in preference to other prophylactic agents because of lesser cost and/or side-effects.
- for travellers to areas with limited/moderate chloroquine-resistant *P falciparum* (e.g. most of the Indian subcontinent, the Philippines and parts of Indonesia – WHO recommendations).

- Therapeutic Guidelines Antibiotic version 14 (2010) no longer includes chloroquine and proguanil as an option for malaria chemoprophylaxis.

There are two problems with this combination:

- Compliance is much more difficult with the combination regimen than with a single drug – it is difficult for travellers to remember to take one drug daily and the other weekly; there is also the possibility of someone confusing the dosing regimens and taking daily chloroquine and weekly proguanil.
- It is not as effective as mefloquine, doxycycline or atovaquone–proguanil.

We use this drug combination extremely rarely.

Side-effects

Proguanil is a safer antimalarial drug. Gastrointestinal side-effects and mouth ulcers appear to be the only significant side-effects. Mouth ulcers occurred in 24% of travellers who received proguanil alone, and in 37% of travellers who received the combination of chloroquine and proguanil. The frequency increased with duration. Hair loss has also been reported with proguanil. The combination with chloroquine, however, causes more gastrointestinal side-effects than either alone.

Precautions

Pregnancy and young children: Safe and well tolerated.

Effect of pregnancy and oral contraceptive pill on plasma level: Recent studies show that plasma concentrations of the active metabolite of proguanil were reduced by approximately 50% in late pregnancy and in women taking the oral contraceptive pill.

Effect on oral typhoid vaccine: Proguanil, possessing antibacterial activity, decreases the immune response to live oral typhoid vaccine. Proguanil should be administered only if 10 days or more have elapsed since the final dose of the vaccine.

Anticoagulant therapy: Proguanil may affect the dose of anticoagulant needed for those on long-term treatment. It is best to stabilise the anticoagulant dose in the presence of proguanil before going abroad.

Primaquine

Dose

- **Adult**: 30 mg base per day taken with food starting 1 to 2 days before entering malaria risk area, continued through exposure and for 1 week after departing a malaria risk area.
- **Children**: 0.6 mg/kg base per day taken with food.

Actions and indications

Primaquine is active against the liver stage of *P vivax* and *P falciparum* (killing developing liver-stage parasites prevents blood-stage formation), blood stage of *P vivax*, hypnozoite stage of *P vivax* and *P ovale*, and gametocytes. It has minor activity against the asexual blood stage of *P falciparum*. It has been used for decades to prevent relapses from *P vivax* and *P ovale* infections or as presumptive anti-relapse therapy (terminal prophylaxis) following heavy exposure of these parasites. Recent studies have demonstrated primaquine to be a very effective and safe (in individuals with normal glucose-6-phosphate dehydrogenase levels) chemoprophylactic agent (Hill 2006).

It has been used with success in partially immune Kenyan children and Indonesian men as prophylaxis with a protective efficacy of 85–95% against both *P falciparum* and *P vivax* infections. In a randomised placebo-controlled trial in non-immune migrants to Papua, primaquine had an overall protective effect of 93%, 88% for *P falciparum* and 92% for *P vivax* (Baird 2001).

Primaquine is not approved in Australia as a prophylactic agent. However, primaquine could serve a useful role when other drugs cannot be used and for travellers with short exposure to high-risk areas as an alternative to atovaquone–proguanil. CDC in its 2010 Yellow Book is recommending primaquine as a first-line prophylactic agent for areas with >90% *P vivax*, e.g. Central America, northern Argentina, Paraguay, and Georgia.

In brief, primaquine is an excellent prophylaxis for areas where *P vivax* is dominant. It is an effective second-line drug against *P falciparum*.

Side-effects

Gastrointestinal: Side-effects such as nausea and abdominal pain are decreased by taking it with food. Taken with food, primaquine causes no more gastrointestinal side-effects than placebo.

Haematological: Haemolysis occurs in glucose-6-phosphate dehydrogenase deficient individuals. Mild methaemoglobinaemia occurs infrequently (<6%) and is transient (<2 weeks), except in individuals deficient in methaemoglobin reductase.

Use during pregnancy: Contraindicated.

Use during breastfeeding: Use only if infant is tested for G6PD deficiency and has normal enzyme levels.

Use in children: May be used in children of any age.

Precautions

Before primaquine is used, G6PD deficiency must be ruled out by appropriate laboratory testing.

Contraindications

- Pregnancy
- Glucose-6-phosphate dehydrogenase deficiency
- NADH methaemoglobin reductase deficiency
- Known hypersensitivity to primaquine or related drugs (e.g. iodoquinol)
- Persons receiving treatment with other potentially haemolytic drugs.

Drug interactions

Primaquine 30 mg/day has caused severe methaemoglobinaemia in HIV-infected individuals when used for prophylaxis of *Pneumocystis jiroveci* (previously *P carinii*) pneumonia, especially in those currently or recently taking dapsone.

Cost of primaquine is similar to atovaquone–proguanil ($60 for 56 tablets).

How to choose malarial prophylaxis

In Australia we have four main choices for malaria prophylaxis:

- doxycycline
- mefloquine
- atovaquone–proguanil
- chloroquine alone.

The fifth option, the combination of chloroquine and proguanil, is seldom if ever used.

The sixth option, primaquine, is not approved for prophylaxis in Australia and is generally considered for use only in areas where *P vivax* predominates.

Doxycycline, mefloquine, and atovaquone–proguanil are more effective than chloroquine alone or in combination with proguanil, in highly chloroquine-resistant areas. These three drugs are regarded as equal in efficacy in places where mefloquine is effective. Doxycycline and atovaquone–proguanil are the prophylactic agents of choice in areas where mefloquine-resistance is common: border areas of Thailand and Myanmar and western Cambodia.

In deciding which regimen to use, a number of factors need to be considered:

- The endemic malarial species and their resistance patterns. Is there falciparum malaria, and is it resistant?
- The risk of malarial transmission. This may vary, depending on the intensity of transmission in the region, the season, and the risk of exposure (urban or rural residence, the type of accommodation and the proximity of mosquito breeding grounds).
- The duration of stay. The longer the stay, the greater the risk of acquisition, but also the greater the problems of compliance and adverse effects.

- The characteristics of the traveller and their relevance in relation to antimalarial drugs. These include age, gender, pregnancy, medical co-morbidities, allergies, previous experience with antimalarial drugs, cost, and likely compliance.
- The availability of reliable diagnostic tests and medical care for malaria. If these are lacking, then more emphasis should be placed on more effective regimens.
- The traveller's preference. It is vital to consider the wishes of the traveller, because the ultimate success of any regimen depends on them.

There are two steps in the process of choosing an antimalarial drug: determine appropriate drug for the area/s to be visited according to the type and intensity of malaria and its resistance pattern, and determine if regimen should be modified.

Step 1: Determining the appropriate drug

The appropriate drug for the area/s to be visited according to the type and intensity of malaria and its resistance pattern is determined with the help of one of three publications: the WHO publication *WHO International Travel and Health*, the US publication *CDC Travelers' Health Yellow Book*, or the British publication *Guidelines for malaria prevention in travellers from the United Kingdom* (Chiodini 2007). Our own 'Malaria risk by country and recommendations' appears in Appendix 4.

One message from these authorities is that not all travellers to countries where malaria exists should automatically be prescribed prophylaxis. This is especially true for tourists and business travellers who will visit only urban areas that are malaria free.

These three publications tell us which regimens are acceptable. They do not take into account contraindications, adverse effects of the drugs, cost, or ease of compliance. We tend to use the CDC recommendation because we seldom use the combination of chloroquine and proguanil.

WHO International Travel and Health

This book is published annually and is an indispensable item for all travel clinics and doctors advising travellers.

The website for the book is <www.who.int/ith/en>.

The site for the countries list is <www.who.int/ith/ITH2010countrylist.pdf>.

The countries document details the type and degree of risk, the season, resistance pattern, and which regimen to use for each country. The information provided for each country also includes the country's stated requirements for mandatory yellow fever vaccination and WHO recommendations for travellers regarding yellow fever vaccinations.

Four types of malaria risk and prevention are categorised:

	Malaria risk	Type of prevention
Type I	Very limited risk of malaria transmission	Mosquito bite prevention only
Type II	Risk of *P vivax* malaria only or fully chloroquine-sensitive *P falciparum*	Mosquito bite prevention plus chloroquine chemoprophylaxis
Type III	Risk of *P vivax* and *P falciparum* malaria transmission combined with emerging chloroquine resistance	Mosquito bite prevention plus chloroquine+proguanil chemoprophylaxis
Type IV	(1) High risk of *P falciparum* malaria in combination with reported antimalarial drug resistance or (2) Moderate/low risk of *P falciparum* malaria, in combination with reported high levels of drug resistance	Mosquito bite prevention plus atovaquone–proguanil chemoprophylaxis, doxycycline or mefloquine (select according to reported resistance pattern)

Note: Type III has the combination of chloroquine and proguanil as one of its choices. The countries where Type III prevention is still an option are parts of Colombia and India, and Nepal, Sri Lanka and Tajikistan. If needed, Type IV prevention can be used instead.

Centers for Disease Control and Prevention (CDC) *Travelers' Health Yellow Book*

The US 'Malaria Risk Information and Prophylaxis, by Country' appears in this (CDC) publication. Information on areas with malaria, drug resistance, malaria species and recommended chemoprophylaxis in each country appears in a table. The website for the table is <wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria-risk-information-and-prophylaxis.aspx>.

- The CDC publication, in a table form, is easy to read. It does not recommend the combination of chloroquine and proguanil as one of its choices.
- For all countries where malaria risk is almost exclusively due to *P vivax*, CDC recommends one of four agents: atovaquone–proguanil, chloroquine, doxycycline, or mefloquine. A fifth drug, primaquine, is also recommenced as an alternative in most of these countries (see CDC table).
- For areas with chloroquine-resistant *P falciparum*, the choice is between doxycycline, atovaquone–proguanil or mefloquine.

Guidelines for malaria prevention in travellers from the United Kingdom

The 2007 British guideline appears in Chiodini (2007).

The website is <www.hpa.org.uk/Publications/InfectiousDiseases/TravelHealth/0701Malariapreventionfortravellersfromthe UK>.

The British recommendation is similar to that of the WHO:

- for areas with chloroquine resistant *P falciparum* the choice is between doxycycline, atovaquone-proguanil or mefloquine
- for areas with little chloroquine resistance the recommendation is the combination of chloroquine and proguanil (some countries in South Asia, South-East Asia and South America)

- for areas without drug resistance the choice is either chloroquine or proguanil.

Step 2: Determine if regimen should be modified.

In the second step, we need to exercise some judgement. We determine if the recommended regimen should be modified, because choosing malaria prophylaxis requires one to balance the risk of death or serious disease from malaria with that of serious side-effects from the drugs.

For most travellers, chemoprophylaxis is largely a choice between doxycycline, atovaquone–proguanil or mefloquine. Very occasionally we would look at whether chloroquine–proguanil could or should be used instead of one of the other three. These issues have already been covered.

The following points are worth remembering when choosing a regimen:

- The decision to use chemoprophylaxis depends on a risk–benefit analysis weighing the risk of malaria against the risk of possible adverse drug reactions. The risk of infection for individual travellers is difficult to quantify precisely, and new at-risk areas may emerge.
- Travellers should take an effective prophylactic agent if visiting high-risk malarious areas, otherwise approximately 1:4000 will die from malaria.
- Mefloquine, doxycycline or atovaquone–proguanil are more effective than the combination of chloroquine and proguanil in these areas.
- All prophylactic antimalarial drugs cause side-effects (as high as 20–40%).
- Most side-effects are mild, and travellers tend to develop tolerance to them after several weeks of use.
- Most travellers tolerate antimalarial drugs well, and fewer than 5% will need to stop the drugs because of side-effects.
- Gastrointestinal symptoms are common, but in only approximately 10% of sufferers will symptoms interfere with daily activities. Symptoms may be minimised by drinking plenty of fluids and taking the drug with food.
- Serious neuropsychiatric side-effects are rare (about 1:10 000).

Table 3.3.2 Factors that influence antimalarial prophylactic drug choice

Factors	(Hydroxy) Chloroquine	Mefloquine	Doxycycline	Atovaquone–proguanil
Dose/administration	Once weekly	Once weekly	Once daily	Once daily
Pre-exposure dosing	7–14 days	7–14 days	1–2 days	1–2 days
Post-exposure dosing	4 weeks	4 weeks	4 weeks	1 week
Drug discontinuation due to adverse events	NA	2–5%	NA	<1%
Cost	cheap	acceptable	acceptable	expensive

Table 3.3.3 Relative cost of antimalarial drugs

	Mefloquine	Doxycycline	Atovaquone–proguanil
$A cost per tablet*	4.50	0.80	5.00
Number of tablets for *x* days	*x*/7 + 7	*x* + 30	*x* + 9
$A cost for 3 days trip	31.50	26.40	60.00
$A cost for 7 days trip	36.00	29.60	80.00
$A cost for 14 days trip	40.50	35.20	115.00

* Cost obtained from a Melbourne hospital pharmacy in mid 2010

- Mild–moderate neuropsychological side-effects occur with both mefloquine and the chloroquine–proguanil combination; opinions differ on the incidence of these reactions, but it is clear that they are far more frequent than in those taking no prophylaxis, taking doxycycline, or taking atovaquone–proguanil.
- About 5–10% of mefloquine users develop adverse reactions sufficiently severe to interfere with daily activities.
- As a rough guide, it is reasonable to regard the incidence of disabling adverse effects of mefloquine to be 0.5% and that of chloroquine–proguanil combination to be 0.25%.
- Atovaquone–proguanil causes the fewest side-effects, but is the most expensive.
- When choosing the appropriate prophylaxis, exclude the regimen that is contraindicated in the traveller, explain the adverse effects to him/her, and let the traveller make the final choice. If the traveller has had no problem with either mefloquine or doxycycline in the past, we would generally stick to that drug.

We are prepared to use mefloquine and doxycycline for >8 weeks; the incidence of side-effects of mefloquine does not vary according to duration of prophylaxis (as described previously, most mefloquine side-effects become apparent in the first few weeks of use). Similarly doxycycline can be used for long periods, provided thrush is not a problem. Atovaquone-proguanil can be taken for prolonged periods, except that its cost is usually prohibitive.

The cost, side-effects, patient preference and contraindications of mefloquine, doxycycline and atovaquone–proguanil determine which drug is best to use.

One of the most difficult questions in malaria prophylaxis today is how to advise travellers who visit low-risk areas, which are often areas with unstable transmission and a changing malaria epidemiology. The CDC approach is to give chemoprophylaxis (atovaquone–proguanil, mefloquine or doxycycline) if the traveller is at risk. The WHO/UK approach is different: chemoprophylaxis is recommended only for high-risk individuals, and stand-by emergency self-treatment (or nothing) is given for low risk travelers.

We generally err on the conservative approach of recommending antimalarials where more than negligible malaria risk exists, although duration of exposure must also be taken into account.

Table 3.3.4 Major contraindications for antimalarial prophylactic drugs

	(Hydroxy) Chloroquine	Mefloquine	Doxycycline	Atovaquone–proguanil
Seizure disorder	Yes	Yes	No	No
Cardiac conduction disturbance	No	Yes	No	No
History of depression, mental illness	No	Yes	No	No
Drug phototoxicity potential	No	No	Yes	No
Yeast infections	No	No	+/–*	No
Pregnancy	No	First trimester#	Yes	No data
Children	No	No	Yes	No

* Relative precaution

Mefloquine is not approved for use during the first trimester in Australia, but WHO and CDC recommend its use if the risk of malaria is high (see section 7.1).

Regimen for chemoprophylaxis: Adults

Areas with chloroquine-sensitive malaria

- chloroquine, 300 mg base/week

Areas with chloroquine-resistant malaria

- doxycycline, 100 mg daily

or

- mefloquine, 250 mg weekly

or

- atovaquone-proguanil, 1 tablet daily

Areas with mefloquine-resistant malaria

- doxycycline, 100 mg daily

or

- atovaquone–proguanil, 1 tablet daily

The combination of chloroquine and proguanil may be used in special circumstances (see under proguanil).

Duration of chemoprophylaxis

- Doxycycline : to start 1–2 days before entering malarious areas and cease 4 weeks after leaving these areas.
- Mefloquine: to start 3–4 weeks before entering malarious areas and cease 4 weeks after leaving these areas.
- Atovaquone-proguanil: to start 1–2 days before entering malarious areas and cease 7 days after leaving these areas.
- Chloroquine: to start 1 week before entering malarious areas and cease 4 weeks after leaving these areas.

Special situations

Pregnancy

See chapter 7.1, The pregnant traveller.

Breast-feeding

Very small amounts of antimalarial drugs are secreted in breast milk. Doxycycline, mefloquine and atovaquone–proguanil should not be used while breast-feeding.

Because the quantity of antimalarials transferred in breast milk is insufficient to provide adequate protection against malaria, infants who require chemoprophylaxis should receive the usual recommended dosages for children.

Children

See chapter 7.2, Children.

Expatriates and long-term travellers

Malaria prevention in travellers staying in malarious areas for a prolonged period is more complicated than for short-term travellers. The following issues are important and must be discussed, with the final choice being made together with the traveller.

Compliance: Compliance with malarial prophylaxis is more difficult for long-term travellers than for short-term travellers. They frequently discontinue chemoprophylaxis prematurely because they perceive the risk to be lower than expected.

Adverse effects of drugs: Although the adverse effects of antimalarials may decrease with time, minor side-effects that normally can be tolerated for some weeks may become such a nuisance in the long term that they lead to non-compliance.

Peer pressure: Travellers frequently compare notes. Stories of neuropsychiatric side-effects from mefloquine heard during travel may cause concern for those who are prescribed the drug.

Local policy: Health authorities in various countries may discourage the use of certain antimalarials as prophylaxis (e.g. in Papua New Guinea, authorities prefer travellers not to use mefloquine for fear of inducing resistance, even though artemisinin derivatives are widely available).

Seasonality of malaria: In many malaria-endemic areas the disease is not a problem in the dry season as there are few mosquitoes around, while in other areas the risk occurs all year round. One needs local knowledge for guidance.

Ease of access to good medical care: This is an important consideration. One can accept a higher risk of malaria if there is good access to timely medical care. Of greatest concern are those who are at high risk and remote from medical care. Highly effective prophylaxis is most important for such individuals (in combination with careful mosquito avoidance, and emergency self-treatment).

Recommendations

1. Take note of the above issues and design the optimal regimen with travellers. Remind travellers that they must take personal responsibility for their health.

2. Prior to their departure, find out, and ask them to find out, if possible:

   – the **availability and standard** of **medical care**, in particular the ability to diagnose malaria, availability of antimalarial drugs, and time and distance away from a medical facility

   – the **incidence, type and seasonality of malaria**

   – **which malaria prophylaxis** is effective and not effective in that area

   – the **frequency and type of malaria** that other expatriates and long-term travellers have experienced.

3. Emphasise the importance of anti-mosquito measures. For those at low–moderate risk of malaria, with good access to medical care, prompt diagnosis and treatment of febrile illness, together with anti-mosquito measures, no chemoprophylaxis may be a reasonable long-term option.

4. If conditions and availability of medical care at the destination are uncertain, it is advisable to begin the expatriate or long-term traveller on a chemoprophylactic agent before leaving for their trip, which they may choose to cease once they become familiar with their new environment and the local medical care options.

5. If malaria is hyperendemic (risk all the year round), adhere to the recommended regimen.

6. Advise expatriates and long-term travellers to bring adequate quantities of antimalarial medications with them. This is because antimalarial drugs (and antibiotics) purchased locally may be counterfeit drugs.

Variations

- **Risk is seasonal**: The traveller may cease prophylaxis for the months when there is no mosquito activity. (For example, this is the practice of many expatriates working in Gambia, who take no malarial prophylaxis during the dry season and mefloquine during the wet.)

- **No or low risk where they live, but high risk periodically during trips away**: They should consider themselves as tourists during those trips and take the best prophylaxis for the trip.
- **Falciparum malaria is prevalent but risk is low and traveller is intolerant or not wishing to take prophylaxis**: Consider emergency self-treatment.

The key to malaria prevention in expatriates and long-term travellers is to provide the travellers with a knowledge and understanding of malaria so that they can take more responsibility for their own health.

Visiting friends and relatives

Immigrants returning to visit friends and relatives are at a greater risk of malaria than are tourists (Keystone 2001). Travellers returning to their countries of origin often believe they are immune to malaria, frequently go to rural areas, and stay for long periods. Unfortunately many of them do not go to their doctor for travel advice and may not realise that any partial immunity they may have developed while living in a malaria-endemic area will wane after migration. These travellers should be made aware of the risks and should have chemoprophylaxis managed the same way as other travellers.

Very short-term travellers

Travellers who spend only a few days in a malarious area require special consideration. These include business travellers, politicians, entertainers, sports people, tourists with stop-overs, pilots, and aircraft attendants. Some make repeated trips.

Taking a prophylactic medication for 5–6 weeks for a trip lasting just a few days may be difficult to accept, and the side-effects of some antimalarials may be detrimental to the purpose of some of these short trips.

The following points are relevant when discussing this issue with short-term travellers:

- Exposure to mosquitoes during short trips is often nil; an important exception is the armed forces spending a few days in a high-risk area. However, one mosquito bite is enough to cause disease (e.g. airport malaria has been acquired in places where malaria is not endemic).
- The main risk to short-term travellers is a short unexpected trip to visit a game park, taking an evening meal in the open, or staying in the rural areas.
- Malaria will not be clinically obvious for at least 1 week. By that time the traveller may well be home.
- After visiting the risky area some travellers may visit malaria-free countries with inaccessible or unreliable medical services, or be in remote areas.

Variations

- Those going on short business trips to cities with a low risk of malaria do not require prophylaxis. They should be reminded to consult a doctor if fever appears. This approach is particularly appropriate for experienced travellers who are familiar with the disease and its treatment.
- For those going to high-risk areas for a short time (for example, reporters going to jungles in South-East Asia, where the attack rate is high even for a short stay) atovaquone–proguanil is ideal. The drug needs to be started only 1–2 days before entering the risk area and ceased 7 days after leaving (considerably shorter than the 4 weeks that doxycycline or mefloquine require after leaving). An alternative is to take nothing while in the risky area and seek medical attention at the first sign of symptoms. If travellers will subsequently be in remote areas, emergency self-treatment should be carried.
- If short trips to high-risk areas are repeated every 3–6 weeks, continuous prophylaxis may be appropriate.
- We do not feel that being in a malarious area for ≤3 nights generally warrants prophylaxis, unless risk is very high or subsequent avoidance of malaria is critical.
- Although business travellers usually stay at night in screened or air-conditioned hotels in cities, risk is not zero as mosquitoes may enter the room during the day, and malaria risk exists in most African and Indian cities. A knockdown insecticide should be sprayed in the hotel room each evening.

Travellers going on cruises

Most travellers on cruises are only ashore during daylight hours when *Anopheles* bites rarely occur; they do not require malaria chemoprophylaxis. However, the cruise itinerary must be reviewed carefully as cruises may have an overnight stay in a malaria-endemic region where malaria chemoprophylaxis would be indicated. All travellers on cruises should use measures to avoid insect bites.

Workers on oil rigs

Oil rigs may be based in river estuaries or many miles offshore. Antimalarial chemoprophylaxis is advised for workers on oil rigs based in river estuaries of malarious countries such as those in West Africa. Offshore rigs pose little risk and antimalarial chemoprophylaxis may only be needed if staying overnight onshore during transit.

Epilepsy

(Hydroxy)Chloroquine and mefloquine are contraindicated for persons with epilepsy. Phenytoin, carbamazepine and phenobarbital reduce the half-life of doxycycline, thereby reducing the effectiveness of its antimalarial activity. A higher than normal dose of doxycycline may therefore be needed if one is taking

any of these anti-epileptic drugs. Although there are no official guidelines available on how much the dose should be increased, the Epilepsy Research Foundation in the United Kingdom recommends doubling the normal dose, i.e. 100 mg twice daily if the traveller is taking carbamazepine, phenytoin or phenobarbital. (Richens 2001). The normal dosage of doxycycline, namely 100 mg once daily, is to be used for travellers taking other anti-epileptic drug(s).

Use proguanil for areas without chloroquine resistance. In areas where chloroquine resistance occurs, atovaquone–proguanil or doxycycline may be used.

Traveller with a history of psoriasis

(Hydroxy)Chloroquine can exacerbate psoriasis and should be avoided in those with a history of generalised psoriasis. Proguanil, atovaquone–proguanil, doxycycline and mefloquine do not cause problems in persons with psoriasis.

Travellers on anticoagulant therapy

Doxycycline and proguanil have been associated with prolonged INR and/or bleeding. The same concern applies to atovaquone–proguanil.

Mefloquine is not considered to be a problem for those taking warfarin, although there is one single case report of bleeding attributed to mefloquine.

No interaction between warfarin and (hydroxy)chloroquine has been documented.

It is best to stabilise the anticoagulant dose in the presence of these drugs before going abroad. Travellers should start taking their malaria tablets at least 1 week (and ideally 2–3 weeks in the case of mefloquine) prior to their departure. A baseline INR should be checked prior to starting chemoprophylaxis, and re-checked after 1 week of taking chemoprophylaxis. If a traveller is away for a long period of time the INR should be checked at intervals at the destination.

Renal impairment

Mefloquine and **doxycycline** are metabolised and excreted through the liver, and can be used. The doses of these two drugs are unchanged for patients on dialysis.

Atovaquone–proguanil contains proguanil and is best avoided in moderate or severe renal failure.

Some (hydroxy)**chloroquine** is excreted in the urine, but most is metabolised in the liver. It can be used in renal insufficiency. Dosage adjustment is required only in severe renal impairment.

Proguanil is excreted by the kidney. If this drug is to be used, reduce the dose according to the following table.

Table 3.3.5 Dosage of proguanil according to renal function

Renal impairment grade	Serum creatinine (μmol/L)	Creatinine clearance (mL/min/1.73 m^2)	Prophylactic dosage of proguanil
None	<150	60	200 mg daily
Mild	150–300	20–59	100 mg daily
Moderate	300–700	10–19	50 mg every 2nd day
Severe	>700	<10	50 mg weekly

Liver disease

Nearly all antimalarials are excreted and metabolised by the liver.

Persons with mild hepatic impairment: atovaquone–proguanil, mefloquine or (hydroxy)chloroquine and/or proguanil may be used. Doxycycline is best avoided.

Persons with moderate hepatic impairment: atovaquone–proguanil, mefloquine or proguanil may be used. Avoid mefloquine, doxycycline and (hydroxy) chloroquine.

In severe liver disease: all antimalarial drugs are contraindicated, with the possible exception of atovaquone plus proguanil.

Travellers taking bupropion hydrochloride to stop smoking

(Hydroxy)Chloroquine or mefloquine should not be used by persons taking Zyban (bupropion hydrochloride SR) as the risk of seizure may be increased.

3.4 Standby emergency self-treatment

Standby emergency self-treatment (SBET) is the self-administration of antimalarial drugs when malaria is suspected and prompt medical attention is unavailable. SBET is only indicated in emergency situations and must be followed by medical consultation as soon as possible.

For high-risk regions such as Sub-Saharan Africa and Oceania the World Health Organization and all national health authorities recommend chemoprophylaxis. However opinions vary for lower risk areas, such as India and border areas of Thailand: some authorities recommend continuous chemoprophylaxis while others recommend seasonal chemoprophylaxis or SBET for these areas.

The following conditions must be met in order for SBET to be contemplated:

- Travellers must understand the various issues involved and be motivated to use emergency self-treatment.
- Sufficient time must be spent with the travellers to inform and instruct them.
- Travellers will or may not have access to good medical care within 24 hours, or be at a place where the ability to treat or diagnose malaria is doubtful.
- SBET is used in conjunction with effective chemoprophylaxis for high-risk travellers.

SBET is recommended for the following groups:

- Travellers who elect not to take prophylaxis
- Travellers who are on no or suboptimal prophylaxis for any reason (for example, contraindications).
- Travellers or expatriates going to destinations where medical facilities and drugs are not of the standard available in the developed world, or to places far away from appropriate medical care. In these situations self-treatment may be life-saving. This would include those on good prophylaxis and going to high-risk areas or areas with high-grade resistance, since effectiveness of prophylaxis is not 100%.

SBET may be considered for the following groups:

- Travellers to areas with low risk.

  Taking antimalarial drugs carries a risk of adverse events, and the risk of infection should be weighed against this risk of adverse events. Most studies find that between 2 and 5% of travellers experience symptoms they consider intolerable. A strong case can be made not to prescribe chemoprophylaxis when the risk of infection is low. How low this risk needs to be before one can adopt this plan of action is not well established: some authorities suggest travel to areas with less than ten malaria cases per 1000 indigenous population per year. (Solomon Islands has the highest risk of 100–200 cases/1000 per year, and Papua New Guinea 10–50 cases/1000 per year) For low-risk malaria-endemic areas of Asia and South America (see page xx at the beginning of this chapter), SBET offers an alternative to taking continuous prophylaxis; this applies particularly to expatriates or long-term travellers.

  SBET for low-risk travel is generally not recommended in the United States or the United Kingdom; it is more popular in Europe. Prior to 2005 we prescribed SBET to few travellers. Greater familiarity with artemether–lumefantrine and atovaquone–proguanil, together with a better understanding of the risk of malaria to travellers, have since enabled us to feel a little more comfortable prescribing SBET, although it should still only be used in carefully selected cases.

Rapid diagnostic test for malaria

Several rapid antigen tests are commercially available in Australia for detection of soluble antigens of *P falciparum* in the peripheral blood. They utilise a finger-prick blood sample, are simple to perform, and give a result in 5 minutes. The tests are species-specific; however, when used for detection of asexual parasites causing clinical disease, false positive tests can occur from rheumatoid factor, gametocytes and residual antigen from infection treated in the preceding month. None of the antigen tests commercially available in Australia has sufficient sensitivity for *P ovale* or *P malariae*, and although they are able to diagnose *P vivax* malaria, their sensitivity is not as high as for *P falciparum* malaria.

Travellers in remote malaria-endemic areas using rapid antigen tests for self-diagnosis frequently fail to diagnose themselves correctly when acutely unwell. Reliance on the test must be cautioned against, as a negative test does not conclusively exclude falciparum malaria, and emergency self-treatment should be taken if the index of suspicion for malaria is high, whatever the test results. While we rarely recommend their use for self-diagnosis, these tests have a place in special circumstances; for example, for expatriate healthcare workers caring for a febrile family member in remote places. In such situations thorough pre-travel instruction on the use of the test is essential. Sourcing kits for travellers may be problematic.

Drugs used for standby emergency self-treatment

All drugs recommended for SBET are effective against both falciparum and non-falciparum malaria. Remember that primaquine should also be given to reduce the relapse risk with vivax and ovale infections.

Artemether–lumefantrine (Riamet/Coartem)

Dose

- **Adult**: 4 tablets twice daily for 3 days, (i.e. a total of 24 tablets). Each tablet contains artemether 20 mg and lumefantrine 120 mg.
- **Children**: Although used safely in children in trials, it is only licensed in Australia for those over 12 years or over 35 kg.

Table 3.4.1 Treatment dose used overseas: daily dose for 3 consecutive days

Body weight (kg)	Daily dose
10–14	1 adult tablet b.d.
15–24	2 adult tablets b.d.
25–34	3 adult tablets b.d.
≥35	4 adult tablets b.d

Use

Artemether–lumefantrine is effective against schizonts and gametocytes of *P falciparum*, and is more rapid in its action than atovaquone–proguanil. There is no clinically significant resistance.

Artemisinin derivatives such as artemether and artesunate are the most rapidly parasiticidal antimalarials, with faster parasite and fever clearance allowing earlier hospital discharge. When used in combination with a second drug (e.g. lumefantrine) only a 3-day course is needed. Because this combination is much better tolerated than quinine, requires a shorter course and is equally efficacious, it has replaced quinine as the treatment of choice for uncomplicated falciparum malaria. In contrast to halofantrine, data to date show no evidence of clinical cardiotoxicity with lumefantrine.

Lumefantrine absorption is influenced by food intake (increasing plasma levels by 16-fold). The manufacturer recommends patients taking some food at dosing times.

Artemether–lumefantrine is now the first-line treatment for travellers with *P vivax* infection returning from the Pacific (Antibiotic Writing Group 2010). It is also our drug of choice as standby emergency self-treatment.

Side-effects

The most common adverse effects are nausea, vomiting and diarrhoea, all of which are also characteristic of acute malaria. The main concern is the possible cardiotoxicity with lumefantrine and neurotoxicity with artemether. There is no real evidence in humans for either of these.

There are no safety data in pregnancy.

Atovaquone–proguanil

Atovaquone–proguanil is licensed in Australia for adults and children ≥11 kg, and is thus useful for use in children 11–35 kg for whom artemether–lumefantrine is not licensed.

Dose

- **Adults**: 4 tablets (each contains 250 mg atovaquone and 100 mg proguanil), i.e. a dose of 1000 mg atovaquone and 400 mg proguanil daily for 3 days.
- **Children**: daily dose for 3 consecutive days.

Body weight (kg)	Daily dose
11–20	1 adult tablet
21–30	2 adult tablets
31–40	3 adult tablets
>40	4 adult tablets

Use

Atovaquone–proguanil is better tolerated than mefloquine or quinine, and is highly efficacious, although occasional resistance has been reported. It should not be used in those who have taken atovaquone–proguanil prophylaxis in the recent past.

There is little to choose between atovaquone–proguanil and artemether–lumefantrine as emergency self-treatment. Both are reliable, even against multi-drug resistant strains of *P falciparum*. They are both well tolerated. The cost per treatment course is similar for the two regimens. Artemether–lumefantrine would be the emergency self-treatment of choice for those taking atovaquone–proguanil as prophylaxis (a situation not very likely to occur).

Mefloquine

Dose

- **Adult**: 750 mg initially, then 500 mg 6–8 hours later.
- **Children**: Initial dose 15 mg/kg up to 750 mg, then 10 mg/kg up to 500 mg 6–8 hours later. Mefloquine is not approved for use in children in Australia, but is used widely overseas.

Use

Treatment with mefloquine is associated with a high risk of adverse drug reactions (28–59%). It causes early vomiting (8% overall, and 20% in children <2 years), and neuropsychiatric effects. The risk of severe neuropsychiatric reactions with a treatment course is 1–3%. Mefloquine is no longer recommended for SBET.

Standby emergency self-treatment regimens

Chloroquine-sensitive areas

For travellers on no prophylaxis in these areas use chloroquine.

Areas with drug-resistant *P falciparum*

Choose one of the following options for uncomplicated falciparum malaria:

- artemether–lumefantrine – our preference
- atovaquone–proguanil.

Steps to take when prescribing SBET

Discuss the following issues with the traveller:

- The incubation period of malaria is at least 1 week, so fever during the first week in the endemic area is not due to malaria.
- If taking self-treatment, seek competent professional medical care within 24 hours. SBET is only a temporary measure and prompt medical evaluation is imperative.
- Symptoms of malaria are entirely non-specific. Fever >38°C (use a thermometer) and symptoms such as shivering, malaise, headache, and myalgia are sufficient for malaria to be considered (advise him/her that malaria may present as florid diarrhoea with fever, and any change in mental state signifies potentially severe disease).
- All travellers should recommence their recommended chemosuppression 1 week after SBET.

Provide the traveller with simple written instructions to guide them in the use of SBET. The following is suggested:

- If you develop a fever of >38°C (use a thermometer) 7 days or more after arriving in a malarious area, seek medical advice at once. If medical help cannot be obtained that day or the condition is deteriorating, emergency self-treatment is indicated.
- Reduce fever (with tepid sponging and paracetamol) as high fever is frequently associated with vomiting, which will impair the amount of medication absorbed.
- Drink plenty of fluid.
- Complete the course of SBET.
- See a doctor at the first opportunity.

3.5 Summary

- We aim to prevent death and severe disease from malaria and not all infection.
- Anti-mosquito measures are vital.
- Fever in a traveller to a malaria-endemic area is malaria until proven otherwise; remind the traveller to seek help promptly (preferably within 48 hours) if they develop a fever.
- Some prophylactic drug is better than none. But, drugs may cause symptoms and ruin a traveller's holiday. Therefore, one must balance the risk of malaria with the risk of side-effects of the drug/s.
- Not all travellers to countries where malaria exists should automatically be prescribed prophylaxis.

- Prescribing for very low-risk and high-risk areas:
  - no prophylaxis may be reasonable for the very low-risk
  - mefloquine or doxycycline or atovaquone–proguanil for high-risk multidrug resistant areas, which are now well known.
- For the rest we have to make a choice.
- Advise travellers to seek medical care after return for up to 12 months if they have a fever and are unwell, and emphasise that they should inform their doctors of the possibility of malaria.

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Chapter 4

Travellers' Diarrhoea

Chapter outline

Diarrhoea is an unfortunate reality of travel, and travellers should expect to encounter the condition. To help travellers prevent and manage diarrhoea you should:

- explain the risk of travellers' diarrhoea
- reinforce the value of eating and drinking safely
- discuss the value of appropriate self-medication
- prescribe a bowel kit consisting of loperamide (Imodium), a course of azithromycin, ciprofloxacin or norfloxacin for those who are able to self-medicate, with additional tinidazole for prolonged or remote travel, and a thermometer
- educate the traveller on how and when to take the various medications.

4.1 Incidence

Diarrhoea is the most common illness of travellers to developing countries. It affects 20–70% of travellers from industrialised countries going to developing countries for periods of up to 2 weeks. Travellers' diarrhoea is part of the broader spectrum of gastrointestinal infections that travellers may experience (Greenwood 2008; Swaminathan 2009) and is the third most common cause of fever in returned travellers, resulting in significant morbidity. In some settings the risk can be extremely high. A study of travellers' diarrhoea on board faluka boats on the Nile in Egypt found an incidence of 90% in the first week. The incidence is highest in the very young and in 15–29-year-olds. The risk of acquiring travellers'

diarrhoea is also higher in those travelling to or residing in developing countries for extended periods of time. A recent study of gastrointestinal infections acquired by travellers reported the highest rates of disease acquisition in travellers returning from South Asia, followed by Sub-Saharan Africa and South America, while travel to Oceania, the Middle East, North Africa, Central America, the Carribbean and South-East Asia is associated with a moderate risk of acquiring a gastrointestinal infection (Map 15) (Greenwood 2008).

4.2 Aetiology

Travellers' diarrhoea has been defined as the occurrence of three or more loose stools per day or any number of loose stools accompanied by abdominal cramps, fever or vomiting.

Bacteria cause approximately 80% of cases of travellers' diarrhoea. Frequently, multiple pathogens are found in the same individual. The most common isolates are enterotoxigenic *Escherichia coli* (ETEC), *Campylobacter* and *Shigella* (O'Brien 2001).

A substantial percentage of travellers' diarrhoea is caused by parasitic organisms, in particular *Giardia lamblia* (most common), *Cyclospora* spp, *Isospora belli*, and *Cryptosporidium parvum* (Freedman et al 2006; Swaminatham 2009). The incubation period for parasite-associated diarrhoea often exceeds the duration of the travel, and parasites are not a common cause of diarrhoea during travel for short-term tourists. Untreated parasite-associated diarrhoea usually lasts longer than 2 weeks.

Viruses are a major cause of diarrhoea and mortality in children residing in developing countries. However, they are responsible for only a minority of cases of travellers' diarrhoea. The most common viral agents include rotavirus, norovirus and adenovirus.

The most commonly encountered microbiologically confirmed pathogens in returned travellers presenting with a gastrointestinal illness are *Giardia lamblia*, *Campylobacter* spp, *Entameoba histolytica* and *Shigella* spp (Swaminathan 2009). The reported rates of specific parasitic, bacterial and viral infections per 1000 returned unwell travellers by geographical region of travel shown in Table 4.2.1 and Maps 16–17 provide a useful guide to assist travel health practitioners in advising travellers of the common infections they may encounter in different travel destinations.

4.3 Prevention

Most diarrhoeal infections are transmitted via contaminated food or water, or food and utensils washed in contaminated water. Prevention is better than cure;

Table 4.2.1 Rates (per 1000 returned unwell travellers) of the most frequently isolated pathogens

Clinically significant IGD pathogen	*n*	% total	Rate per 1000 returned unwell travellers[a]
Giardia	810	27.9	31.3
Campylobacter	384	13.2	14.8
Entamoeba histolytica	363	12.5	14.0
Shigella	182	6.3	7.0
Strongyloides	176	6.1	6.8
Salmonella spp other	134	4.6	5.2
Dientamoeba fragilis	116	4.0	4.5
Ascaris	110	3.8	4.3
Salmonella typhi	99	3.4	3.8
Hookworm	71	2.4	2.7
Tapeworm	71	2.4	2.7
Hepatitis A virus	67	2.3	2.6
Trichuris trichura	52	1.8	2.0
Salmonella paratyphi	47	1.6	1.8
Clostridium difficile	38	1.3	1.5
Enterobius	36	1.2	1.4
Cryptosporidium	32	1.1	1.2
Cyclospora	31	1.1	1.2
Hepatitis E virus	31	1.1	1.2
Yersinia spp (non-pestis)	20	0.7	0.8
Clonorchis	19	0.7	0.7
Fasciola	5	0.2	0.2
Trichomonas intestinalis	4	0.1	0.2
Isospora	3	0.1	0.1
Vibrio cholerae	1	0.0	0.0
TOTAL	**2902**	**100**	**112.2**

a From single or multiple regions

Source: Swaminathan 2009

however, adhering to dietary advice is often difficult. The cumulative percentage of those who transgress one or more dietary guidelines increases with duration of stay, and even the motivated well informed traveller is likely to lapse within two weeks.

General measures

The following general measures may reduce the risk of acquiring diarrhoea:

- Choose food that is freshly and thoroughly cooked and served steaming hot.
- Avoid food cooked earlier in the day that then tends to sit at room temperature until served, food that is re-heated, and food that is not hot.
- Choose well-prepared local dishes with a high turnover in a busy restaurant, rather than unusual dishes of low turnover and uncertain age.
- Avoid intricate dishes that require much handling in preparation, or have stood at room temperature for prolonged periods, or may have been in contact with insects or animals. (Hamburgers may be very dangerous as they are frequently pre-cooked and kept at room temperature for a long time.)
- Avoid shellfish, prawns and meat that has not been thoroughly cooked. It is even safer to avoid shellfish and prawns completely: even well-cooked oysters can transmit hepatitis A virus. Methods commonly used to cook oysters, such as grilling, steaming, stewing and frying, do not reliably inactivate noroviruses.
- Only eat fruit and vegetables that you can peel or cut open yourself, such as banana, citrus fruits, papaya. Avoid uncooked leafy vegetables and salads.
- Dry foods such as bread and jellies or syrups (which are hyperosmolar and do not support bacterial growth well) are generally safe.
- Boil drinking water. Bottled or canned beverages are safe. You can easily tell if carbonated drinks have been freshly opened. Ice is only as safe as the water from which it is made.
- Avoid milk, ice-cream, yogurt drinks and other milk products including cheeses, unless made with pasteurised or boiled milk.
- Check out how and where food is prepared.
- Wash your hands with soap and water before eating or preparing food.
- A simple adage is: cook it, peel it, or forget it.

A problem that is difficult to counteract is what happens to the food after it has been prepared and before it gets into a person's mouth. The food handler's hygiene habits are a crucial factor; freshly cooked food contaminated by dirty fingers prior to coming to the table is as risky as uncooked food.

Water treatment

Boiling

Boiling is the only completely reliable way to purify water. Boiling for 10 minutes at sea level will kill most organisms, while boiling for 20 minutes will also

kill most parasites including *Ascaris lumbricoides*. Such boiling is often impractical and is not necessary to render water safe to drink. In fact, boiling for any length of time kills all bacteria.

Water must be heated to above 65°C to reliably kill bacterial pathogens. The water temperature in hot water taps is seldom above 65°C. If there is no means to boil water, maintaining water temperature at 60°C for a prolonged period is an alternative.

At sea level, protozoal cysts, including *Giardia*, *Entamoeba histolytica* and *Cryptosporidium*, are killed rapidly at 55–60°C. Similarly, most helminth eggs and larvae are killed at this temperature.

- Boiling time: Allow 1 minute for each 300 metres (1000 feet) above sea level. In general, bringing water to a brisk boil will make the water safe to drink. When in doubt, it is best to boil it for 1 minute.

We generally recommend bringing water to a brisk boil and covering it while it stands to cool; covering water keeps it hotter for substantially longer.

Disinfectants

Chemical disinfection with a halogen (iodine and chlorine) is effective in killing bacteria and viruses. The sensitivity of infectious agents to halogenation (from most to least sensitive) is: enteric bacteria > viruses > protozoan cysts > bacterial spores > parasitic larvae and ova. *Cryptosporidium* and *Cyclospora* are halogen resistant.

Both chlorine-based and iodine-based disinfection tablets are available commercially. Iodine preparations are generally more effective than chlorine-based ones, especially against viruses such as hepatitis A, and amoebic cysts. Manufacturers' instructions should be followed carefully. The concentration and duration of treatment is critical and varies depending on the degree of faecal contamination, cleanliness, and temperature of the water. Due to the variables involved, many authorities discourage chemical treatment of water as a means of purification.

Iodine

Betadine antiseptic solution (containing 1% available iodine), dispensed in a small plastic bottle, is convenient. Add 8 drops of Betadine antiseptic solution to 1 litre of clear water (20 drops for cold or cloudy water). Tincture of iodine, containing 2% iodine, can be used as an alternative; 5 drops of the tincture should be added to 1 litre of clear water (10 drops for cold or cloudy water).

Treated water should be allowed to stand for 20–30 minutes before use. Very turbid or cold water may require prolonged contact time; if possible allow several hours prior to use. Travellers with thyroid disease, or those who are pregnant or allergic to iodine, should not use this disinfectant.

Adding vitamin C (50 mg per litre) to water treated with iodine, but only after iodine treatment has been completed, eliminates the taste and colour of the iodine. It is a good idea to carry two drink bottles – one for disinfection with iodine and the second for iodine-treated water with added vitamin C ready for drinking.

Long-term use of iodine can be a concern, and it should probably not be used regularly for more than 3–6 months at a time.

Chlorine

Chlorine is an effective disinfectant against bacteria and some viruses, although it is less effective than iodine against amoebic cysts and it is more readily inactivated by organic material present in water. Standard methods of water disinfection with chlorine do not eliminate *Giardia* cysts. 'Puritabs' are available commercially (1 tablet per 1 litre of water). Two drops (0.1 mL) of 5% chlorine bleach to one litre of water and allowed to stand for 30 to 60 minutes at room temperature will render water safe to drink.

Filtration

A variety of commercially produced portable filters are currently on the market. A filter must have an absolute pore size ≤0.2 microns in order to filter pathogenic bacteria. *Giardia* and amoebic cysts are easy to filter as they are 5–8 microns in size. However, viruses are more than 8 times smaller than a 0.2 micron filter pore, so they readily pass through. This is why chemical treatment is necessary in addition to filtration in the developing world.

Filtration is useful when one is concerned about two particular protozoa: *Cryptosporidium* and *Cyclospora*. For their filtration use filters with a 1 micron pore size.

Although silver-based iodide-impregnated resins and micropore filters (mostly ceramic) kill and/or remove many microorganisms, few published reports evaluate their effectiveness. Filters vary considerably in size, fragility, maintenance and replacement requirements, and are often expensive (as much as $300 in Australia). However, for trekkers they may provide a practical method of reducing the risk of enteric infections when boiling water is difficult or impossible. On the basis of limited efficacy data, we prefer filters utilising an iodine-impregnated silver resin.

Vaccination

Effective vaccines to prevent travellers' diarrhoea are not yet commercially available. However, the WC-rBS cholera vaccine, Dukoral, has been shown to produce up to 60% reduction in diarrhoea caused by heat-labile toxin-producing enterotoxigenic *E coli* (LT-ETEC). This is particularly important as up to 20% of travellers' diarrhoea acquired in developing countries is caused by LT-ETEC.

Although the vaccine is only 60% effective against LT-ETEC this would still be expected to prevent around 10% of travellers' diarrhoea. Vaccination should be considered as an adjunctive measure for the prevention of travellers' diarrhoea in high-risk travellers such as those with underlying inflammatory bowel disease or immunosuppression. In Australia, Dukoral vaccine is only registered for the prevention of cholera and not LT-ETEC.

4.4 Management

Most episodes of diarrhoea are short-lived and require no treatment. The need to treat diarrhoea depends on its severity, persistence, inconvenience, and the presence of conditions associated with an increased risk of severe disease or complications (e.g. diabetes, renal disease or immunosuppression). Travellers should be educated on the symptoms of dehydration and managment with oral rehydration suspensions.

Fluids

Replacement of fluids lost as a consequence of diarrhoea is more important than drugs. The majority of travellers do not develop diarrhoea that is severe enough to result in dehydration, and simple measures (including bottled or canned beverages, tea, broth or adequately treated water) that ensure an adequate fluid intake are sufficient. Milk and milk products are best avoided as these may worsen symptoms, and caffeine and alcohol may exacerbate dehydration.

Children with diarrhoea are of special concern. The younger the child, the more rapidly dehydration can occur. A child's fluid loss is best replaced with a commercially prepared oral rehydration solution (ORS) such as Gastrolyte. Adults travelling with young children (particularly under the age of 2 years) are advised to carry sachets of these with them. If this is not available, use one of the dilutions of drinks described in the discussion of travellers' diarrhoea in chapter 7.2.

For a child who is vomiting, frequent small sips of ORS should be given. Medical advice is mandatory should the child show signs of significant dehydration with marked listlessness, decreased urine output, or a very dry mouth. Medical advice should also be sought for diarrhoea of more than 24 hours duration in an infant aged less than 1 year. (See travellers' diarrhoea in chapter 7.2.)

Food

Food is important in maintaining the body's energy stores and healing the bowel. Light carbohydrate-rich foods are tolerated best: rice, bananas, papaya (pawpaw), potatoes, and dry biscuits. Breast-fed children should continue being breast-fed. Bottle feeds or solids should be stopped for no longer than 24 hours, and preferably not at all. Young children should continue an intake of food, and solids such as potato and pumpkin or cereals such as rice are suitable. Multiple small meals are better than a few large ones.

Self-treatment

Antimotility drugs ('stoppers')

Loperamide (Imodium) and diphenoxylate (Lomotil) are antimotility agents and do not eradicate the infective organisms. These drugs slow down the bowel's muscle contractions so there are fewer bowel actions, but the patient continues to lose fluid into the bowel. This may lead to an underestimate of the degree of dehydration.

Loperamide modestly lessens the amount of fluid loss into the bowel (diphenoxylate has no antisecretory activity), has fewer side-effects (both opiate-related and anticholinergenic side-effects can occur with diphenoxylate) and is the preferred drug. Both drugs can be dangerous in children.

These agents are generally reserved for patients with mild diarrhoea and, since most diarrhoeal illnesses last only a few days, these drugs may be very helpful in relieving diarrhoea and cramps.

When antibiotics are appropriate, antimotility drugs can safely and effectively be combined with them in most situations, with more rapid relief than either antibiotics or loperamide alone.

Antimotility drugs **should not** be:

- given to those with high fever (over 38°C) or with blood in the stool (i.e. dysentery)
- used for longer than 48 hours
- used in children <6 years or in pregnant women.

Loperamide has caused ileus and drowsiness in very young infants. In Australia, loperamide is contraindicated in children <12 years of age. In the United Kingdom the lower age limit is 4 years, and in the United States loperamide is not given to infants <2 years of age. Antiperistaltic agents should generally be avoided in children with travellers' and other infectious diarrhoea, but, if necessary, can be given to children aged 6 years and over.

- **Loperamide** (adult dose): 2 capsules statum (each 2 mg) followed by 1 capsule after each unformed stool (maximum 8 capsules per day).
- **Loperamide** (child dose; ≥6 years of age): maximum 0.8 mg/kg/day, given in three divided doses.
- **Diphenoxylate**: (≥6 years of age) no more than 2 tablets (each 2.5 mg) four times per day (maximum 8 tablets per day).

Antibiotics

Most travellers' diarrhoea is mild and self-limited, and antibiotics are not generally needed. However, because most episodes are due to bacteria, antibiotics are often effective and have an important role in the treatment of more severe or

prolonged diarrhoeal illnesses. An effective antibiotic will relieve symptoms and shorten the duration of illness, particularly in cases of *Shigella*- and *E coli*-associated diarrhoea.

Diarrhoea pack for travellers

Loperamide + azithromycin, norfloxacin or ciprofloxacin + thermometer + tinidazole (for prolonged/remote travel) + ORS (for children and high-risk travellers)

Antibiotics are recommended for cases where the diarrhoea is:

- accompanied by a fever >38°C and/or blood in the motion
- moderate to severe (>3 or more loose stools in a 24-hour period, with distressing symptoms)
- fails to improve after 1–2 days.

It may be unreasonable to wait 24 hours before treatment. If diarrhoea has a sudden onset and the traveller is significantly uncomfortable, diarrhoea can be assumed to have a bacterial cause and be treated accordingly (see Table 4.4.2).

Most diarrhoeal illnesses that are not dysenteric respond to a single-day antimicrobial treatment. This is sufficient in approximately 85% of cases.

For severe disease or if fever or bloody stools are present, the antibiotic should be continued for 3 days and medical advice may be required.

For less severe disease, antibiotic treatment for 24 hours may suffice, but a 3-day course should be taken if symptoms are not clearly better within 24 hours.

In the absence of fever or bloody stools, loperamide can be used together with an antibiotic.

In brief, **self-treat when there is fever, blood in stools or severe symptoms, or when more than three unformed stools have been passed within 12–24 hours**. If the traveller is at increased risk of severe or complicated diarrhoea, such as immunocompromised patients, the elderly, or those with diabetes or vascular disease, it is appropriate to be more aggressive in the treatment of diarrhoea. Such patients should be advised to commence antimicrobial therapy after passing the first or second loose stool.

Azithromycin

This new macrolide is effective against *E coli*, *Salmonella*, *Shigella*, *Vibrio cholerae* and *Campylobacter* species, including multiresistant *Shigella* and *Salmonella* and quinolone-resistant *Campylobacter* that are now prevalent throughout South-East Asia and India. It is the drug with the broadest activity against the bacterial pathogens causing travellers' diarrhoea. However, resistance of *Campylobacter* species to azithromycin has already been reported.

A randomised double blind trial comparing various treatment regimens of azithromycin and levofloxacin in travellers demonstrated a superior cure rate at 72 hours after receiving a single 1000 mg dose of azithromycin (96%) compared to 3 days of 500 mg daily azithromycin (85%) and 3 days of 500 mg daily levofloxacin (71%) (Tribble 2007). The single-dose regimen was also effective in travellers' diarrhoea associated with fever, severe diarrhoea, and bloody diarrhoea. The group given a single dose of 1000 mg azithromycin did have a higher rate of nausea.

For the treatment of travellers' diarrhoea in an *E coli* predominant region of the world, a single 500 mg dose of azithromycin is as effective as a 1000 mg dose. Azithromycin, 500 mg per day for 1–2 days, appears to be effective in most cases of travellers' diarrhoea. Loperamide plus 500 mg of azithromycin is more effective than either dose of azithromycin alone.

With increasing rates of quinolone resistance in developing countries, the simplicity of a highly effective single dose treatment with azithromycin makes this antimicrobial a reasonable first-line agent for the treatment of travellers' diarrhoea.

- **Azithromycin** (adult dose): 1000 mg as a single dose or 500 mg daily for 3 days
- **Azithromycin** (child dose): 10 mg/kg daily for 3 days (maximum dose: 500 mg daily).

Fluoroquinolones

Fluoroquinolones, such as norfloxacin or ciprofloxacin, are effective antibiotics against the majority of the bacterial pathogens causing travellers' diarrhoea. Unfortunately, with increasing usage, many organisms, especially *Campylobacter* and *Salmonella* species, have developed resistance to them. This is especially so in Thailand, India and Nepal.

A 3-day course generally suffices for the treatment of diarrhoea, and is as effective as longer courses. Single-dose therapy is adequate in most cases; however, for bacteria such as *Campylobacter* and *Shigella dysenteriae*, single-dose therapy may be inadequate. If evidence of invasive disease exists, such as high fever, chills, or bloody diarrhoea, a 3-day course of treatment should be taken.

Norfloxacin is cheaper than ciprofloxacin and is equally effective in travellers' diarrhoea (as are other fluoroquinolones). With its higher blood level, ciprofloxacin is the preferred antibiotic for the treatment of typhoid fever, and for severe diarrhoea in the immunocompromised host.

Fluoroquinolones are safe and well tolerated. Concern about damage to bone and cartilage in children is overrated. It is based on theoretical concerns and exceptions can be made in an emergency. Fluoroquinolones are safe for children

over the age of 8 (see chapter 7.2), but they are contraindicated in pregnant women. Disadvantages of their use include drug interactions, such as those with warfarin and anticonvulsants.

- **Norfloxacin** (adult dose): 1 tablet (400 mg) twice daily on the first day, followed, if needed, by 1 tablet (400 mg) twice daily for a further 2 days.
- **Ciprofloxacin** (adult dose): 1 tablet (500 mg) twice daily on the first day, followed, if needed, by 1 tablet (500 mg) twice daily for a further 2 days.

Choice of antibiotic

The choice of antibiotic for the empiric treatment of travellers' diarrhoea depends on a number of factors: age of the patient, pregnancy status, destination of travel, drug allergies, known bacterial resistance patterns, and other medications used by the traveller.

In most parts of Latin America and Africa, enterotoxigenic *E coli* and enteroaggregative *E coli* are the major pathogens encountered; either one of the quinolones or azithromycin is appropriate. In Asia, invasive pathogens (*Shigella*, *Salmonella*, and *Campylobacter* species) appear to be more common causes of travellers' diarrhoea than for travel to other regions of the world; for this region azithromycin is the drug of choice.

Azithromycin appears to be the drug of choice for treatment of febrile dysentery in the traveller for whom the expected cause of illness is *Campylobacter* or *Shigella* species.

Azithromycin may be a drug of choice in treating travellers' diarrhoea in children because of its safety, tolerability, and ease of administration, and for pregnant women, in whom the use of fluoroquinolones is contraindicated.

Rifaximin

Rifaximin is a non-absorbable semisynthetic antibiotic derived from rifamycin. It has a broad antimicrobial spectrum that includes most Gram-positive and negative bacteria. The drug is active against the common aetiological agents associated with travellers' diarrhoea including ETEC and *Campylobacter* spp. In clinical trials rifaximin has been shown to be more effective than co-trimoxazole and equivalent to ciprofloxacin for the treatment of travellers' diarrhoea. To date resistance to rifaximin has not yet been described, but extensive clinical data is still lacking. The drug is not yet available in Australia but holds promise as an effective treatment modality.

Treatment for prolonged diarrhoea

When diarrhoea is prolonged, in spite of antibiotic treatment, parasites become a possibility; *Giardia lamblia* is the most common cause. In contrast to bacterial diarrhoea, protozoal diarrhoea generally begins slowly, with 1 or 2 loose stools,

Table 4.4.2 Treatment of travellers' diarrhoea in adults

Clinical syndrome	Recommended treatment
Mild • 1–3 watery stools/24 hours • tolerable symptoms • no blood in stools • no fever	• None • loperamide if needed
Moderate • >3 loose watery stools/24 hours • tolerable symptoms • no blood in stools • no fever	• loperamide • if symptoms present >1 day, take – azithromycin 1000 mg in a single dose OR – azithromycin 500 mg; if no improvement after 24 hours, continue azithromycin 500 mg daily for 2 more days OR – one of the quinolones, two tablets 12 hours apart on the first day; if no improvement after 24 hours, continue the quinolone 12 hourly for a further 2 days
Moderate–severe • >5 watery stools/24 hours • distressing symptoms (e.g. abdominal cramps, vomiting) • no blood in stools • no fever	• loperamide + – azithromycin 1000 mg in a single dose OR – azithromycin 500 mg; if no improvement after 24 hours, continue azithromycin 500 mg daily for 2 more days OR – one of the quinolones, two tablets 12 hours apart on the first day; if no improvement after 24 hours, continue the quinolone 12 hourly for a further 2 days
Dysenteric • bloody stools or fever • temperature ≥38°C	• Take – azithromycin 1000 mg in a single dose – or azithromycin 500 mg daily for 3 days – or one of the quinolones 12 hourly for 3 days • avoid use of loperamide

and an absence of fever or vomiting. Self-treatment with tinidazole or metronidazole may be warranted in patients who have suspected *Giardia* or have failed to resolve their symptoms with quinolone antibiotics. It is also important to stress that symptoms of diarrhoea may persist even after adequate clearance of a pathogen with antibiotics. Up to 20% of travellers who have suffered from an infective cause of diarrhoea will have residual symptoms, including loose bowel actions and abdominal cramps, that may persist for up to 6 months after the resolution of the infection. A small number of these patients may have other underlying gastrointestinal pathology such as inflammatory bowel disease, and

therefore further investigations are required if symptoms persist for 6 months or more.

Giardia lamblia

Giardia lamblia is a common problem for travellers, and one of the major causes of parasitic diarrhoea globally (Map 16). In developing countries giardiasis has peak prevalence rates of up to 20% in children under 10 years of age (Gilman & Brown 1985). Giardiasis is an important cause of chronic diarrhoea in travellers returning from developing countries, with infection rates of 1–3% in short-term travellers to endemic areas (Kelsall 1992). Infection most commonly occurs through ingestion of contaminated water, although other modes of transmission include the consumption of contaminated food and person-to-person spread.

Giardiasis has a median incubation period of 7–10 days (range 3–25 days or longer). Diarrhoea occurring in the first 3 days of travel is unlikely to be giardiasis. The onset of giardiasis is gradual. Symptoms commonly include mild–moderate diarrhoea and upper abdominal discomfort with a bloated sensation, anorexia, and offensive belching and flatus. Chronic infection may result in malaise, epigastric discomfort, steatorrhoea, and lactose intolerance. However, contrary to popular belief, there are no symptoms specific for giardiasis. Giardiasis should be considered in travellers who have been at their destination for 4 days or more before the onset of diarrhoea. If diarrhoea does not improve after 2–3 days or more, especially if it has not responded to antibiotic treatment, self-treatment for possible *Giardia* infection is recommended, especially for those far from medical care.

- Adult dose (tinidazole): 4 × 500 mg tablets (2 g) orally as a single dose
- Child dose (tinidazole): 50 mg/kg up to a maximum of 2 g.
- Child dose (metronidazole): 30 mg/kg up to 2 g orally, given in three separate doses, daily for 3 days.

These regimens produce cure rates of 80–90% in both adults and children. Pregnant women however should not receive these antibiotics. Paromomycin 500 mg orally qid for 7 days can be used in this setting, but this is effective in only 60–70% and repeat treatment may be necessary. Albendazole (400 mg twice daily for 3–5 days) may also be effective in refractory cases but is not recommended in pregnancy. Nitazoxanide is also effective against *Giardia lamblia* but is not readily available and is not recommended in pregnancy.

Alcohol should be avoided when taking these drugs as the combination produces a disulfarim-like adverse reaction.

Entamoeba histolytica

Almost all amoebic infections present as chronic, low-grade diarrhoea, which is intermittent (diarrhoea for 1–2 days followed by 1–2 days absence, then recurrence). Weakness and fatigue are frequent associated symptoms.

Severe amoebic infection (i.e. amoebic dysentery), characterised by severe cramping abdominal pain, tenesmus and rectal pain, multiple small volume, often bloody, stools, is rare. The syndrome with this clinical picture is usually due to *Shigella* dysentery.

Treatment is with metronidazole: 600 mg, three times per day for 7–10 days (taken after meals), or tinidazole 2 g once daily for 3 days (adult dose). This may not eradicate amoebic cysts. Patients with amoebiasis should be followed up on return, and given a luminal amoebicide. Diloxanide furoate was an effective cysticidal agent but is no longer available. An alternative to diloxanide is paromomycin, 500 mg orally 8-hourly for 7 days. Continuing diarrhoea, particularly if severe, worsening or bloody, requires medical attention.

Other forms of chronic diarrhoea

Chronic diarrhoea is common in travellers spending a prolonged period in developing countries, and may persist despite treatment for the above two organisms. *Cyclospora* and *Cryptosporidium* are now recognised causes of diarrhoea in the traveller and stool investigations looking specifically for these pathogens should be ordered (e.g. modified acid fast stain, cryptosporidial antigen).

Travellers with repeated episodes of diarrhoea, especially if prolonged or dysenteric, or persistent symptoms, should have a check-up on return to Australia. Irritable bowel syndrome and tropical sprue will need to be considered. In patients >50 years of age, great care should be taken to exclude colonic or other malignancy before a diagnosis of irritable bowel syndrome is made.

4.5 Chemoprophylaxis

Some travellers request chemoprophylaxis. Although this is seldom required, it may be appropriate for certain patients travelling to high risk destinations even for relatively short periods of a few days.

Concerns relating to antimicrobial prophylaxis for travellers' diarrhoea include:

- adverse reactions
- development of antimicrobial resistance or microbial overgrowth resulting in infection with resistant organisms
- confusion and uncertainty about how to treat illness that occurs despite antimicrobial prophylaxis.

Emerging antimicrobial resistance in developing regions is primarily related to the use and abuse of antibiotics by the indigenous population. Tourists probably contribute little to this problem.

The use of antimicrobial prophylaxis may also give travellers a false sense of security that tempts them to be less stringent with dietary precautions.

Reasonable indications for consideration of antimicrobial prophylaxis include patients:

1. with AIDS and other immunocompromising conditions
2. with inflammatory bowel disease
3. with cardiac or vascular disease who are taking diuretics
4. with insulin-dependent diabetes
5. who have had a gastrectomy or use potent H2 blockers or proton-pump inhibitors
6. for whom the purpose of the trip is critical and who are unwilling to risk illness.

The antimicrobial agents that are effective as prophylaxis are norfloxacin (400 mg daily) or ciprofloxacin (500 mg daily). Rifaximin is also very effective as a prophylactic agent; however it is not available in Australia. There is little data at present to support the use of azithromycin for chemoprophylaxis. Travellers should begin the drug on their first day in the country and continue it for 1–2 days after leaving. The maximum duration should be 3 weeks.

Travellers who develop moderate–severe diarrhoea despite prophylaxis should be advised to increase the dose to full therapeutic doses and seek medical help if symptoms do not abate.

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Chapter 5

Non-vaccine-preventable Infections

Chapter outline

There are many potentially serious infections that may pose a risk to travellers and for which no vaccines are available. Following discussions on vaccines, malaria prevention and travellers' diarrhoea at the consultation, the travel-medicine practitioner should identify other infectious risks that may apply to the traveller, whether because of destination/s and duration of travel, occupational or other activities, or individual susceptibility. Information should be provided about these infections, their relevance, modes of transmission and methods of prevention, or the traveller should be referred to an authoritative source of information.

In this chapter advice will be given on both destination- and activity-related infections. The risk, distribution, and methods of prevention of a number of specific infections for which no vaccines are available will then be outlined.

5.1 Destination

Certain infections are restricted to specific geographical locations, so knowledge regarding regions in which particular diseases can be acquired is important when advising travellers. Appendix 1, Common travel destinations, lists the important infectious hazards of the common destinations.

5.2 Types of activities

Infections may be transmitted sexually, parenterally, by ingestion, by inhalation, by a percutaneous route or via an insect vector. Thus, the following activities or behaviours may put the traveller at risk of certain specific infectious agents:

- eating and drinking
- exposure to insects
- recreational, occupational and animal exposures
- sexual encounters
- substance abuse
- contact with blood
- exposure to infectious aerosols.

Relevant infections/infestations and their geographical distributions are outlined in Tables 5.2.1–5.2.4. The importance of safe behaviour in these areas is emphasised in Chapter 1 (see section 1.7). After determining which infections the traveller may be at risk of contracting, advise the traveller according to the information under each specific infection outlined in this chapter.

Infections acquired via ingestion

The most common health problem acquired via ingestion is travellers' diarrhoea. This topic is addressed in detail in Chapter 4, which also describes general food and water hygiene measures that should be followed by all travellers, particularly those going to developing countries. Table 5.2.1 sets out the important infections that can be acquired by ingestion of specific foods.

Vector-borne diseases

Many infections (see Table 5.2.2) are transmitted by the bite of an insect, and vector-borne infections are among the most common cause of fever in returned travellers. Mosquitoes are the main insect vector of disease, but there are many other insect vectors, including ticks, flies, fleas, sandflies, lice and triatomine bugs, that may be responsible. The same preventive measures are generally effective against all of them:

- covering up with long sleeves and long pants
- applying DEET-containing repellent on bare skin
- sleeping in screened accommodation or under a mosquito net (preferably permethrin-impregnated)
- impregnating clothing and bed sheets with permethrin.

Diseases transmitted via recreational and occupational activities

A number of recreational and occupational activities (see Table 5.2.3) can put travellers at risk of infections, many of which are transmitted by the percutaneous route. To minimise exposure to these infections:

Table 5.2.1 Food and drink

Significant exposures	Infections	Main geographic sites
Unpasteurised milk or cheese	Brucellosis	Worldwide, especially Mediterranean countries, Middle East, and Central and South America
	Listeriosis	Worldwide
	Salmonellosis	Worldwide
	Q fever	Worldwide
Raw or undercooked fish or seafood	Hepatitis A	Worldwide
	Vibrio spp	Worldwide
	Paragonimiasis	Mainly Asia (especially China, India, Myanmar), also Latin America and Africa
	Clonorchiasis	Asia, especially China, Japan, Taiwan, Korea, Vietnam, Laos, Cambodia
	Gnathostomiasis	South-East Asia
Raw or undercooked meat	Salmonellosis	Worldwide
	Campylobacter spp.	Worldwide
	Pathogenic *E coli* and other bacterial infections	Worldwide
	Trichinosis	Widespread, especially Asia and Mexico
	Toxoplasmosis	Worldwide
Watercress, raw salads	Fascioliasis	South America, Caribbean, Australia, Asia, Middle East, France

- avoid walking barefoot, especially in areas with potentially contaminated soil; shoes, sandals or sneakers should be worn
- avoid swimming in beaches that might be contaminated with human sewage or with dog faeces, as this can be a source of many infections
- avoid swimming, wading or canoeing in fresh water that may be a source of infections including schistosomiasis and leptospirosis
- avoid direct skin contact with sand as this may lead to exposure to cutaneous larva migrans. Travellers should be advised to wear clothes or to lie on a towel or blanket.

Exposure to soil, excavations and caves may also be a source of infections such as endemic fungi. Thus, whenever possible, tourists should avoid dust exposure in contaminated areas.

Table 5.2.2 Vector-borne infections

Insect vector	Infections	Main geographic sites
Mosquitoes	Malaria	Many tropical areas – see Chapter 3, Malaria prevention
	Dengue fever	Tropics of Asia, Africa, Central and South America, Pacific
	Chikungunya	Most of Sub-Saharan Africa, India, South-East Asia, Indonesia and Philippines
	Viral haemorrhagic fevers	Different species in different countries – mainly Africa, South America, South-East Asia
	Lymphatic filariasis	Different species in different tropical areas, especially Pacific Islands, Asia, Africa, South America
	Japanese encephalitis	South-East Asia, Pakistan, Sri Lanka, Bangladesh, Papua New Guinea, Torres Strait Islands
	Yellow fever	Limited to areas in Africa and South America
Ticks	Rickettsial spotted fevers	Worldwide – different species in different areas
	Lyme disease	North America, Europe, Russian Federation, China, Japan
	Ehrlichiosis	Mainly south-eastern, south-central, north-eastern and mid-Atlantic regions of the United States
	Babesiosis	North-eastern United States (Massachusetts, New York City, Rhode Island and Connecticut) and Europe (especially France, Great Britain and Ireland, Sweden, Spain, Portugal and Germany)
	Tularaemia	North America, Central Europe, former Soviet Union, China, Japan
	Congo–Crimean fever	Africa, Middle East, Russia, China
	Tick-borne encephalitis	Central Europe (Austria, Germany), Russian Federation, United States
	Endemic relapsing fever	Tropical Africa, Spain, Saudi Arabia, India, Central Asia, North and South America
Tsetse fly	African trypanosomiasis	Tropical Africa, especially Uganda, Angola, Democratic Republic of Congo, Sudan
Triatomine ('kissing') bugs	American trypanosomiasis	Mexico, Central and South America
Sand-fly	*Bartonella bacilliformis*	Mountain valleys of Peru, Ecuador and Colombia
	Leishmaniasis (cutaneous and visceral)	Different species in different areas, especially Central/South America, Middle East, Asia, India, Mediterranean region, Sub-Saharan Africa
	Sandfly fever	Mediterranean region

Table 5.2.2 Vector-borne infections (Continued)

Insect vector	Infections	Main geographic sites
Fleas	Plague	Western United States, South America, Africa, South-eastern Europe, South-East Asia, Russian Federation
	Murine typhus (*Rickettsia typhi*)	Worldwide
	Cat-scratch *(Bartonella henselae)*	Worldwide
Mites	Scrub typhus (*Rickettsia tsutsugamushi*)	Mainly tropical Asia, Pacific Islands, northern Australia
Black flies	Onchocerciasis	West and Central Africa, Latin America, Arabian peninsula
Lice	Epidemic relapsing fever	Ethiopia, Sudan, Central Africa, South America, Asia
	Epidemic typhus (*Rickettsia prowezakii*)	Mexico, Central and South America, Africa, Asia
	Trench fever (*Bartonella quintana*)	Worldwide
Horse and deer flies	Loiasis	Limited to Western and Central Africa

Many infections including rabies, anthrax and others are transmitted by animals. Travellers should avoid animal bites or scratches by abstaining from feeding, patting, playing, or interacting with animals.

Diseases transmitted via sexual or parenteral exposure

People are at risk of sexually and/or parenterally transmitted infections (see Table 5.2.4) both at home and during travel, but may be more likely to engage in unsafe behaviour while travelling. Therefore the importance of safe behaviour during travel needs to be emphasised.

5.3 Specific infections

African trypanosomiasis ('sleeping sickness')

Organism

Trypanosoma brucei gambiense (West African trypanosomiasis) or *Trypanosoma brucei rhodesiense* (East African trypanosomiasis).

Geographical distribution

- Tropical Africa between latitudes 15°N and 20°S, especially remote and rural regions where tsetse flies are prevalent.
- Epidemic disease in certain provinces in Angola, Democratic Republic of Congo, Sudan and Uganda

Table 5.2.3 Recreational, occupational or animal exposures

Significant exposures	Infections	Main geographic sites
Swimming, rafting, bathing in fresh water	Schistosomiasis	South America, Caribbean, Africa, Middle East, East Asia, Philippines
	Leptospirosis	Worldwide
	Free living amoebae	Worldwide
Soil exposure or digging	Coccidiodomycosis	Southern United States, Central America, Mexico, Venezuela, Colombia, Paraguay, Argentina
	Paracoccidiodomycosis	Tropical Americas, especially Brazil
	Blastomycosis	Mainly central/south-eastern United States, Canada, Zaire, Tanzania, South Africa
	Penicilliosis	South-East Asia
	Melioidosis	Mainly South-East Asia (especially Thailand), tropical Australia
Cave exploration	Histoplasmosis	Worldwide, particularly in North and South America, East Asia, Africa
Walking barefoot or lying on soil/sand	Strongyloidiasis	Mainly humid tropical areas
	Cutaneous larva migrans	Tropical areas
Animals or animal products	Brucellosis	Worldwide, especially Mediterranean countries and Central/South America
	Q fever	Worldwide
	Anthrax	Worldwide, especially South/Central America, Asia, Africa, southern and eastern Europe
	Tularaemia	North America, Central Europe, former Soviet Union, China, Japan
	Plague	Western United States, South America, Africa, south-eastern Europe, South-East Asia, Russian Federation
	Rabies	Worldwide except countries listed in Table 2.13.1
	Toxoplasmosis	Worldwide
Rodents	Hantavirus	China, South Korea, United States (especially Four Corners area), South America
	Plague	Western United States, South America, Africa, south-eastern Europe, South-East Asia, Russian Federation
	Murine typhus (*Rickettsia typhi*)	Worldwide
	Viral haemorrhagic fevers	Different species in different countries, e.g. Lassa fever in West Africa
	Lassa fever	West Africa, especially Sierra Leone, Guinea, Liberia, Nigeria

Table 5.2.4 Sexual or parenteral exposures

Significant exposures	Infections	Main geographic sites
Sexual contacts	HIV, hepatitis B, syphilis, gonorrhoea, chlamydia etc.	Worldwide
Transfusions, injections, body piercing, tattoos	HIV, hepatitis B, hepatitis C	Worldwide

- Moderate–low prevalence in Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Guinea, Gabon, Ghana, Kenya, Mali, Mozambique, Nigeria, Tanzania, Togo and Zambia.

Transmission and risks to travellers

Transmitted via the bite of an infected tsetse fly. This rare infection in travellers is usually due to East African trypanosomiasis (due to *T brucei rhodesiense*), which occurs in eastern and southern Africa.

Travellers to urban areas are not at risk. Humans are exposed to bites while hunting or on wildlife safari in game park areas, especially near Lake Victoria or in parks in Sub-Saharan Africa (including Serengeti, Ngoro Ngoro, Amboseli, and Akagera). A cluster of East African disease has occurred from Tanzania.

Illness

Travellers with East African disease often have a very short incubation period (few days) and present acutely with fever, a transient morbilliform rash, and meningoencephalitis, with progressive neurologic involvement over 1–4 weeks. Ultimately coma and death ensue. West African trypanosomiasis causes a more chronic infection, which may not result in neurological involvement for years.

Prevention

Tsetse flies are active during the day, and are attracted to large moving objects and dark blue colours.

- Wear long-sleeved shirts and long pants in endemic areas.
- Avoid bright-coloured clothing.
- Keep car windows closed and don't ride in open vehicles.
- Permethrin and DEET have some value, but are not always effective.
- There is no vaccine or preventive drug available.

American trypanosomiasis (Chagas' disease)

Organism

Trypanosoma cruzi.

Geographical distribution

- Found only in south and central America.
- Endemic areas in Argentina, Brazil, Bolivia, Belize, Chile, Colombia, Costa Rica, Ecuador, El Salvador, French Guiana, Guyana, Guatemala, Honduras, Mexico, Nicaragua, Uruguay, Paraguay, Peru, Panama, and Venezuela.

Transmission and risks to travellers

Transmitted by the triatomine bug ('kissing bug'), a small insect that lives in crevices of dirt walls and roofs of rural dwellings. It usually feeds at night. Travellers sleeping in local adobe huts in rural areas or areas off the normal tourist track may be at risk. Visitors to large cities or remote jungle ruins are not at risk. Oral transmission can also occur via ingestion of foods contaminated with triatomines or their faeces.

Illness

Early infections are usually asymptomatic. The long-term complications of infection include cardiomyopathy and paralysis of the intestines and oesophagus ('megaoesophagus' and 'megacolon').

Prevention

- It is best to avoid living in or camping near adobe huts. If it not possible to avoid sleeping in a hut, sleep in the centre of the room away from the walls.
- Nocturnal application of insect repellents and sleeping under a mosquito net will also help prevent bites.
- Travellers staying in hotels or resorts are NOT at high risk for contracting the disease.
- Blood transfusions should be avoided in endemic areas.
- There is currently no vaccine or preventive drug for Chagas' disease.

Amoebiasis

Organism

The protozoon *Entamoeba histolytica*.

Geographical distribution

E histolytica has a worldwide distribution. It is endemic in Africa, Mexico, and Central and South America.

Transmission and risks to travellers

It is transmitted by ingestion of contaminated water.

Illness

Several forms of the disease are recognised:

1. A noninvasive disease producing luminal intestinal disease (causing abdominal bloating, cramps and diarrhoea) is most frequent.
2. Amoebic colitis produces severe, bloody diarrhoea. Toxic megacolon with gastrointestinal haemorrhage, perforation and death may occur.
3. An extraintestinal infection. This most commonly manifests as liver abscesses.

Prevention

Avoid uncooked food and contaminated water (see Chapter 4, Travellers' diarrhoea).

No vaccine is available.

Brucellosis

Organism

There are different species, but the major travel- and food-related infection is caused by *Brucella melitensis*.

Geographical distribution

Endemic in Mediterranean countries (especially Greece, Spain, Italy and Portugal), the Middle East (especially Iraq, Iran and Kuwait), India, and Latin America (especially Peru, Argentina and Mexico).

Transmission and risks to travellers

Different species are transmitted in different ways, including inhalation of infected aerosols, direct contact with infected animals, and ingestion of unpasteurised dairy products. *B melitensis* is particularly associated with ingestion of contaminated goats' milk or cheese.

Illness

Acute infection is associated with fever, myalgia, arthralgia, and organomegaly. Relapsing forms and chronic infection can lead to complications such as arthritis, spondylitis, orchitis, uveitis and depression.

Prevention

- Avoid contact with livestock.
- Avoid ingestion of unpasteurised dairy products.

Chikungunya virus

Organism

Caused by the Chikungunya virus, which is an alphavirus.

Geographical distribution

Chikungunya fever has long been known to be endemic in tropical Africa and Asia. The virus is present throughout much of Africa, with transmission thought to occur mainly between mosquitoes and monkeys. After a long period of absence, outbreaks of Chikungunya fevers appeared in Indonesia in 1999, and in 2006 reappeared in India and various Indian Ocean islands, including Comoros, Mauritius, Reunion and Seychelles (see Map 20.) In some areas attack rates have been over 45%. Chikungunya fever displays interesting epidemiological profiles, as major epidemics appear and disappear cyclically, usually with an inter-epidemic period of 7–8 years and sometimes as long as 20 years.

Transmission and risks to travellers

Transmitted by *Aedes* mosquitoes (*Aedes aegypti* and *Aedes albopictus*). Popular travel destinations have been affected by recent outbreaks. As a result more than 1000 European and American travellers returned with Chikungunya fever in 2006–07. A number of cases of Chikungunya have also been diagnosed in travellers returning to Australia. In 2007, local European transmission of Chikungunya virus occurred in north-eastern Italy.

Illness

The name Chikungunya is derived from an African word meaning 'that which bends up'. The clinical manifestations of this illness range from a syndrome not unlike Ross River virus to a more severe presentation resembling dengue fever (see below). Common symptoms include fever, polyarthralgia/arthritis, gastrointestinal symptoms, maculopapular skin rash and conjunctivitis. It is usually a self-limiting illness that has an incubation period of two to four days. Serious complications, such as neuroinvasive disease, occur rarely. There are no specific treatments for Chikungunya virus infection.

Prevention

The only way to prevent infection is to avoid mosquito bites as there is no vaccine currently available. Recovery from infection provides lifelong immunity. All travellers to endemic areas should use personal insect protective measures such as:

- remaining in well-screened or completely enclosed air-conditioned areas.
- using insect repellent on exposed skin.
- wearing clothing that reduces the amount of exposed skin.
- using aerosol insecticides indoors.
- eliminating any standing water in and around the dwelling where *Aedes aegypti* may breed, such as uncovered water containers, pot plant bases, roof

gutters, drains, containers, tyres, or depressions in the ground (see also Chapter 3, Malaria prevention).

Ciguatera

Toxin-mediated disease

Ciguatera is a form of seafood poisoning caused by eating subtropical or tropical marine fish (e.g. barracuda, red snapper and grouper) that accumulate naturally occurring toxins through their diet.

Geographical distribution

Found in warm-water fish near coral reefs between 35°N and 35°S latitude, it is particularly common in the Pacific Islands and the Caribbean. In Australia, it occurs throughout North Queensland as far south as Bowen, in southern Queensland around Hervey Bay, around the eastern tip of Arnhem Land, and around Groote Eylandt in the Gulf of Carpenteria.

Transmission and risks to travellers

Humans may contact the toxin by eating herbivorous fish or by consuming carnivorous fish that, in turn, have eaten herbivorous fish. The likelihood of ciguatoxin being present and the concentration of ciguatoxins increases with larger carnivorous fish. Not all fish of a given species or from a given locality will be toxic. Areas may become toxic or lose toxicity over time. Freshwater fish are free from ciguatera. As warm-water fish are commonly eaten outside the tropics, the disease can be seen outside endemic areas.

Illness

Initial signs of poisoning usually occur within 6 hours and almost always within 24 hours after consumption of toxic fish, and include numbness and tingling of the lips, tongue and throat, which may spread to the extremities, a peculiar metallic taste, dry mouth or hypersalivation. Other symptoms include dizziness, malaise, muscle and joint pain and rash.

- In many cases, especially with mild poisoning, the earliest symptoms are **gastrointestinal** (i.e. sudden abdominal cramps, nausea, vomiting, and watery diarrhoea).
- **Neurological** symptoms include intensified distal paraesthesiae, headache, blurred vision, vertigo, and muscular weakness to the point of prostration. Altered perception of hot and cold and acute dysaesthesia to cold are distinctive symptoms. Distal sensory loss and loss of deep tendon reflexes are typical findings.
- **Cardiovascular** manifestations include arrhythmias, bradycardia or tachycardia (typically), atrioventricular block, hypotension, and myocardial depression.

The illness is usually self-limiting, and symptoms often subside within several days of onset. Gastrointestinal and cardiovascular features rarely last beyond 24–48 hours, although there is a low incidence of death resulting from respiratory and cardiovascular failure. Neurological symptoms, particularly dysaesthesia and weakness, commonly persist for many days or weeks (occasionally months), as do general symptoms of malaise, lassitude and disturbed sleep. Mannitol infusion (1 g/kg intravenously over 30–60 minutes) can dramatically cure ciguatera symptoms, especially if given early for more serious cases. Recovered patients commonly experience relapse of symptoms months to years after recovery, particularly following consumption of alcohol or fish (even fish that is not demonstrably toxic).

Prevention

- Avoid eating warm-water fish from near shore, especially coral reef fish.
- Avoid eating large coral reef fish (>2.5 kg), including sharks.
- Do not eat internal organs of fish as toxins tend to collect in these.
- Check with knowledgeable locals about toxic fish and toxic seasons.
- Eat a small piece of a fish at the first sitting. Wash fish flesh prior to consuming (this may reduce the amount of toxin in the flesh of herbivorous fish).

Cutaneous larva migrans (CLM)

Organism

Larval stages of animal hookworms (usually the dog or cat hookworm).

Geographical distribution

Occurs worldwide but found mainly in warm, humid climates. Common on coasts of Africa, South-East Asia, India, Malaysia, Sri Lanka and Thailand.

Transmission and risks to travellers

Larvae directly invade skin. Seen most commonly in children or sunbathers walking barefoot or sitting on damp contaminated ground.

Illness

CLM is one of the most common dermatologic problem in travellers to tropical countries. It typically causes a very itchy serpiginous track, usually on the foot or lower extremity.

Prevention

- Wear shoes or sandals and avoid skin contact with soil in endemic areas.
- Prevent children from running around barefoot on the beach.
- Use a beach mat or towel when sunbathing.

Dengue fever

Organism

Caused by a flavivirus with four serotypes (Den 1, Den 2, Den 3 and Den 4).

Geographical distribution

Occurs in tropical and subtropical countries of Asia and Africa, and also in the Caribbean and Central and South America (Map 21). The risk to travellers is greatest in the Indian subcontinent, South-East Asia, Southern China, Central and South America (except Chile, Paraguay and Argentina), the Caribbean (except Cuba and the Cayman Islands), Mexico and Africa. There is a somewhat lower risk for travellers to Taiwan and the Pacific Islands, and even lower for the Middle East. Importation resulting in local transmission occurs periodically in North Queensland.

Transmission and risks to travellers

Dengue is transmitted by the bite of the *Aedes* mosquito (*Aedes aegypti* and *Aedes albopictus*). These mosquitoes tend to live in and around human habitation, breeding wherever fresh water collects. Thus dengue is predominant in urban centres, but may also be found in rural areas. It is rarely found at elevations >1300 m (4000 ft). *Aedes* mosquitoes are most active in the early morning and late afternoon, but they may feed at any time during the day, especially indoors, in shady areas, or during overcast periods.

A marked increase in cases has been observed over the past decade in most countries of the tropics and explosive outbreaks occur. Epidemic transmission is usually seasonal, during and shortly after the rainy season. More severe forms of the disease (i.e. dengue haemorrhagic fever (DHF) or dengue shock syndrome) are very rare among travellers. The risk of DHF for travellers who have had past dengue and go back to an endemic area during an outbreak is in the region of 0.5–1.0%. Adults are likely to be at the lower end of this range.

Illness

Dengue is generally an acute biphasic illness characterised by fever, headache, retro-orbital pain, severe aching of muscles and bones, and rash. It should be suspected in patients presenting with these symptoms, particularly if they also have thrombocytopenia. If the patient develops fever more than 2 weeks after the last potential time of exposure, dengue can be eliminated from the differential diagnosis. Complete recovery can take 2–4 weeks.

While the disease is often mild and self-limiting, it may present in a severe form associated with haemorrhagic complications, shock, and in some cases, death. When complications arise, they most frequently occur 3–7 days after the onset of symptoms. Warning signs for complications include abdominal pain developing after the third day of illness and a falling platelet count. One severe form,

called **dengue haemorrhagic fever**, is more common in persons <15 years of age and in those having their second or subsequent infection. A second severe form is known as **dengue shock syndrome** (DSS). The case-fatality rate of DHF and DSS in most countries is about 5%. Mortality in both severe forms is dramatically reduced by good supportive medical care.

Dengue fever can cause an acute febrile illness in pregnant women and sepsis-like illness in neonates. However, no differences in rates of preterm birth, postpartum haemorrhage, low birth weight, or neonatal outcomes have been observed, and there are no long-term sequelae.

Prevention

The only way to prevent infection is to avoid mosquito bites as there is currently no vaccine commercially available. Recovery from infection provides lifelong immunity against that serotype, but confers only partial and transient protection against subsequent infection by the other three serotypes. All travellers to endemic areas should use personal insect protective measures. They should:

- remain in well-screened or completely enclosed air-conditioned areas
- use insect repellent on exposed skin
- wear clothing that reduces the amount of exposed skin
- use aerosol insecticides indoors
- eliminate any standing water in and around the dwelling where *Aedes aegypti* may breed, such as uncovered water containers, pot plant bases, roof gutters, drains, containers, tyres, or depressions in the ground (see also 'Minimising exposure to mosquitoes' in chapter 3.2).

Hepatitis E

Organism

Hepatitis E virus.

Geographical distribution

Mainly seen in areas with inadequate environmental sanitation, especially Asia, Africa, the Middle East and Central America.

Transmission and risks to travellers

Transmitted by the faecal–oral route through drinking contaminated fluids (especially water) and less frequently by eating contaminated food. Hepatitis E is the most common type of acute viral hepatitis in many developing countries, and has been responsible for a number of large outbreaks in refugee camps.

Illness

Clinically indistinguishable from hepatitis A. Complete recovery is the rule and there is no long-term carrier state. High fatality (15%) occurs in pregnant women, and fetal loss is common.

Prevention

- Avoid drinking water (and beverages with ice) of unknown purity.
- Avoid eating uncooked shellfish and uncooked, peeled fruit and vegetables.
- There is no vaccine available.

Legionellosis (Legionnaires' disease)

Organism

Various *Legionella* species, particularly *L pneumophila*.

Geographical distribution

Worldwide distribution. Many cases are acquired in Europe, particularly around the southern Mediterranean.

Transmission and risks to travellers

Transmission is via the airborne route. Travel is emerging as a strong risk factor for the acquisition of legionnaires' disease. Individuals staying in resort hotels, on cruise ships, or using spa facilities are at highest risk.

Illness

Initial stage characterised by anorexia, diarrhoea, malaise, myalgia, headache and nonproductive cough. Can progress to consolidation and even respiratory failure.

Prevention

- Monitoring and cleaning of cooling towers and water systems is recommended to decrease the risk of disease acquisition.
- There is no vaccine available.

Leishmaniasis (cutaneous and visceral)

Organism

Various *Leishmania* species.

Geographical distribution

Leishmaniasis can be classified geographically into New World (Central/South America) and Old World diseases. *Leishmania* organisms are endemic in scattered foci in >80 countries on every continent except Australia, Oceania and

Antarctica. More than 90% of cutaneous infections occur in the Middle East, Saudi Arabia, Iran, Peru, Afghanistan, and Brazil. More than 90% of visceral infections occur in Bangladesh, India, Sudan and Brazil. Infections also occur in southern Europe, particularly in Spain, Italy, and southern France.

Transmission and risks to travellers

Transmitted by sand-flies, which usually are most active from dusk to dawn, Leishmaniasis occurs predominantly in individuals living in endemic regions, but travellers to these areas can also be infected, even after <1 week of exposure. Leishmaniasis is more common in rural than urban areas.

Illness

Clinical findings can be divided into cutaneous, mucocutaneous, or visceral manifestations. Cutaneous lesions can have a wide range of appearances, but typically cause either 'wet' or 'dry' ulcers. In visceral leishmaniasis, splenomegaly, fever, and cachexia are common. Many infections are asymptomatic.

Prevention

In endemic areas, preventive measures include vector control, control of animal reservoirs, and early diagnosis and treatment of cases. No vaccine or chemoprophylaxis is available.

In travellers, personal protective measures against sand-fly bites are most effective:

- Avoid outdoor activities, especially from dusk to dawn.
- When outside, wear long-sleeved shirts, long pants, and socks.
- Apply insect repellents containing DEET on uncovered skin.
- Spray clothing with permethrin-containing insecticides.
- Use a bed net if sleeping in an unscreened room.

Leptospirosis

Organism

Spirochete, *Leptospira interrogans*.

Geographical distribution

Worldwide, but mainly in the tropics.

Transmission and risks to travellers

Transmitted when skin or mucous membranes come into contact with water, moist soil or vegetation contaminated with urine of infected animals or rodents. Occupational hazard for field workers, farmers, abattoir workers, and others who have contact with urine or tissues of contaminated animals. Travellers who

bathe, wade or raft in contaminated waters are at potential risk. An outbreak occurred in athletes participating in Eco-Challenge-2000 in Borneo, Malaysia. Hiking in jungle areas during the rainy season is also high risk for exposure.

Illness

Typically a biphasic illness characterised by fever, headache, abdominal pain, severe myalgia and conjunctival suffusion. It can be complicated by meningitis, vasculitis, nephritis, hepatitis, myositis, conjunctivitis, myocarditis, arthritis, haemorrhage, respiratory distress and confusion. The time between exposure and symptom onset is 2 days to 4 weeks.

Prevention

- Avoid recreational water activities such as swimming or wading in endemic areas.
- Wear protective clothing.
- Vaccination against specific serovars is available for limited immunisation of those with occupational exposure, but is not recommended for travellers.
- Doxycycline prophylaxis (200 mg weekly beginning 1–2 days before exposure and continuing through the period of exposure) can be considered for those at high risk but is rarely indicated.

Lyme disease

Organism

Borrelia burgdorferi, a Gram-negative spirochaete (spiral-shaped bacteria).

Geographical distribution

Clinically confirmed cases of Lyme disease have been reported all over Eurasia, as well in the United States and Canada. It is the most commonly reported tick-borne infection in Europe and North America. The abundance of reservoir hosts (usually small and medium-sized animals, including birds) in a particular habitat is the most important factor in the establishment of significant infected tick populations.

Transmission and risks to travellers

It is transmitted during the blood feeding of ticks of the genus *Ixodes*. Ticks thrive in conditions found in temperate deciduous woodland, so disease can occur in hikers or campers. Tick activity is the greatest in spring and early summer.

Illness

Infection can be subclinical (asymptomatic), or have a range of clinical presentations. Clinical presentations can generally be divided into three stages but progression from an early to later stage is not inevitable, even if the infection is untreated.

1. **Early localised Lyme borreliosis**: Approximately 60% of cases develop erythema migrans, a characteristic red rash or lesion spreading from the site of a tick bite. The affected patient may also have vague 'flu-like' symptoms.

2. **Early disseminated Lyme borreliosis**: The organism may spread to other tissues via the bloodstream and lymphatics. Manifestations of this stage include multiple areas of erythema migrans (usually smaller than the initial lesion), facial palsy, cranial nerve lesions, aseptic meningitis, encephalitis, arthritis, and carditis.

3. **Late Lyme borreliosis**: Progression to this stage is uncommon but may occur in patients who were not treated or inadequately treated at an earlier stage. The most frequent manifestations include chronic arthritis, acrodermatitis chronica atrophicans (widespread atrophy of the skin), and meningoencephalitis.

Prevention

- Avoid walking or camping in wooded areas during spring/summer.
- Promptly remove an attached tick if you notice it.
- Prophylactic treatment with an antibiotic is not generally recommended for a tick bite.
- A vaccine was produced but is no longer manufactured and is not available.

Lymphatic filariasis, loiasis and onchocerciasis

Organism

Lymphatic filariasis is caused by one of three lymphatic-dwelling filarial parasites, namely *Wuchereria bancrofti*, *Brugia malayi* or *Brugia timori*. Loiasis is caused by the parasite *Loa loa*. Onchocerciasis is caused by the parasite *Onchocerca volvulus*.

Geographical distribution

W bancrofti occurs in Sub-Saharan Africa, South-East Asia, the Indian subcontinent, many of the Pacific Islands, and focal areas in Latin America. *B malayi* occurs mainly in China, India, Malaysia, the Philippines, Indonesia, and various Pacific Islands. *B timori* is limited to the island of Timor (Indonesia and East Timor). Loaisis is limited to rainforests of West and Central Africa. Onchocerciasis is limited to rural areas of tropical Africa (particularly in Nigeria and Zaire), the Arabian peninsula (Yemen), and Latin America (Brazil, Colombia, Ecuador, Guatemala, southern Mexico, and Venezuela). Within endemic regions, the infection has a focal distribution that coincides with areas conducive to breeding sites for the mosquito vector.

Transmission and risks to travellers

Lymphatic filariasis is spread by the bite of a mosquito harbouring infective larvae. Loaisis is transmitted by deerflies or horseflies. Onchocerciasis is transmitted by the bite of a blackfly. These infections are rare in short-term travellers (<3 months), but the risk increases with length of stay.

Illness

Most infections are asymptomatic. Specific syndromes associated with lymphatic filariasis include acute adenolymphangitis, filarial fever and tropical pulmonary eosinophilia. Lymphatic obstruction may lead to permanent changes of elephantiasis, but this occurs mainly in individuals from endemic areas with high worm burdens, not in travellers. Infected travellers instead may demonstrate an allergic-type reaction to developing larvae that is characterised by a local eosinophilic infiltrate, causing lymphangitis, lymphadenitis, urticaria, and rash. Loiasis causes episodic swellings ('Calabar swellings') or subconjunctival migration of the adult worm. Onchocerciasis in travellers generally causes a nonspecific dermatitis that can be intensely itchy. Ocular and skin complications are very rare, except in natives of endemic regions.

Marked peripheral eosinophilia is a feature of these diseases in travellers (may exceed 3000/μL).

Prevention

Protection against insect bites is most important.

- Sleep under a mosquito net.
- Use mosquito repellent on exposed skin between dusk and dawn.
- Diethylcarbamazine 300 mg taken once a week during the period of risk is effective in preventing filarial infection (but is not recommended for routine travellers).
- No vaccines for these infections are available.
- In endemic areas, prevention relies on vector control or on mass chemotherapy programs.

Melioidosis

Organism

Burkholderia pseudomallei.

Geographical distribution

Mostly found in South-East Asia, particularly in Thailand. Also occurs in northern Australia and West Africa. The organism has a widespread distribution in soil, stagnant water and rice paddies in endemic areas.

Transmission and risks to travellers

Infection is acquired via contact of broken skin with contaminated soil, via aspiration or ingestion of contaminated water, or via inhalation of dust from soil. Infection in short-term travellers is uncommon.

Illness

Infection may be asymptomatic, lead to isolated pulmonary disease, or be disseminated and cause multi-organ involvement and overwhelming sepsis. Typical respiratory symptoms are cough, chest pain and occasionally haemoptysis. Chronic abscesses and osteomyelitis can result. Diabetics, people who abuse alcohol, and the immunosuppressed are at greatest risk of symptomatic infection. Reactivation of latent infection can occur, with progressive immunosuppression.

Prevention

Avoid exposure to soil and rice paddies in endemic areas, especially if diabetic, immunosuppressed, or open wounds are present.

Myiasis (cutaneous)

Organism

Two species of fly that cause cutaneous myiasis are *Cordylobia anthropophaga* (Tumbu fly) and *Dermatobia hominis* (botfly).

Geographical distribution

The Tumbu fly exists throughout Sub-Saharan Africa. The human botfly is endemic throughout Central and South America.

Transmission and risks to travellers

Larvae of both species can attach to and penetrate the intact skin of healthy hosts, producing furuncles.

Illness

The Tumbu fly skin lesion starts as a papule, which may be itchy or pricking. As the papule grows, the lesion resembles a boil. After 8–12 days, larvae emerge from the skin. Lesions may involve any part of the body, but usually occur on the back, head or neck.

The botfly skin lesion begins as a pruritic erythematous papule which appears within 24 hours of infestation. As larvae develop subdermally over 6–12 weeks, lesions enlarge with local inflammatory reaction and increasing local symptoms. When mature larvae work their way to the skin, significant local pain can develop and movement can be sensed within the skin.

Both types of larvae can be induced to emerge from the skin by covering the lesion with an occlusive material (e.g. paraffin oil or Vaseline) to restrict the oxygen supply.

Prevention

Prevention of Tumbu fly infestation:

- Avoid playing or sleeping on the ground.
- Dry clothes indoors with the window closed or screened to prevent contact with flies.
- Iron all clothing, sheets and towels with a hot iron on both sides to kill emerging larvae.

Prevention of botfly infestation:

- Avoid insect bites by using personal protection measures, repellents and clothing.

Q fever

Organism

Coxiella burnetti.

Geographical distribution

Occurs on all continents. Animal reservoirs are cattle, sheep and goats.

Transmission and risks to travellers

Transmission is generally by airborne dissemination of organisms in dust, so the disease can occur in people without direct animal contact. Direct contact with contaminated straw, wool, hair and hides can also transmit Q fever. Raw milk from infected cows contains organisms, and may be another source of infection.

Q fever is mainly an occupational disease of the meat industry and of farmers. Disease in travellers is uncommon, but travellers can contract the infection through direct or indirect contact with animals, e.g. visiting farms or attending agricultural shows.

Illness

Q fever can present as an acute febrile illness or as a chronic relapsing disease. The chronic form usually presents as a chronic relapsing febrile illness, although rarely may present as a culture-negative endocarditis.

Prevention

- Avoid animal contact.
- An effective vaccine is available for those at occupational risk, but is not recommended for travellers.

Rickettsial infections

Spotted fevers

Organism

Examples include *Rickettsia rickettsii* (Rocky Mountain spotted fever), *Rickettsia conorii* (Mediterranean spotted fever), *Rickettsia africae* (African tick bite fever) and *Rickettsia australis* (Queensland tick typhus).

Geographical distribution

R rickettsii is present throughout United States, and also in Mexico and South America. *R conorii* is present in Africa, India, the Mediterranean region, and the Middle East. *R africae* is present in Sub-Saharan Africa (especially Botswana, Zimbabwe and South Africa). *R australis* is present in Queensland, New South Wales, Tasmania and eastern Victoria.

Transmission and risk to travellers

Transmitted by tick bites. Occasionally occurs in travellers who spend time trekking or camping, or on safari in grassy areas where ticks are prevalent.

Illness

Fever, malaise, myalgia, headache, and maculopapular rash are typical. Often there is an eschar at the site of the tick bite.

Prevention

- Avoid tick bites by using repellents and wearing protective clothing.
- If exposed, prompt detection and tick removal is important.
- No commercially available vaccine.

Typhus group

Organism

Rickettsia prowazecki (epidemic typhus), *Rickettsia typhus* (murine typhus).

Geographical distribution

R prowazecki is worldwide. *R typhi* is also worldwide, but in focal areas.

Transmission and risk to travellers

R prowazecki is spread by the body louse. It tends to occur in epidemics, associated with poor hygiene and in impoverished populations. *R typhus* is spread by rat fleas and often occurs following exposure to rat-infested buildings. Neither is seen commonly in travellers.

Illness

Headache, fever, myalgia, lymphadenopathy, and macular rash are common.

Prevention

- Avoid vector-infested habitats.
- Use repellents and wear protective clothing when exposed.

Scrub typhus

Organism

Rickettsia tsutsugamushi.

Geographical distribution

R tsutsugamushi exists in the South Pacific, Papua New Guinea, South-East Asia and East Asia, including China, Korea and Japan, and tropical northern Australia (Kimberley region of Western Australia, Top End of the Northern Territory, especially Litchfield Park, coastal northern Queensland north of Townsville, and the Torres Strait Islands).

Transmission and risks to travellers

Scrub typhus is transmitted by mites. The larval form of the mite lives in grass and attaches to passing humans or animals. The mite goes unnoticed because of its small size. Disease occurs in people who engage in outdoor occupational or recreational activities, and so can be seen in travellers who hike or camp in grassy areas.

Illness

Abrupt onset of fever, lethargy, myalgia, cough, photophobia, headache, vomiting and conjunctivitis. Maculopapular rash (50%) occurs 7 days after the onset of the illness. An eschar is often present with associated lymphadenopathy.

Prevention

- Avoid vector-infested habitats.
- Use repellents and wear protective clothing.

SARS (severe acute respiratory syndrome)

Organism

Caused by a coronavirus, called the SARS-associated coronavirus (SARS-CoV).

Geographical distribution

SARS was first reported in Asia in February 2003. Over the next few months, the illness spread to more than two dozen countries in North America, South America, Europe, and Asia before the outbreak was contained. The countries most heavily affected included China, Hong Kong, Vietnam, Taiwan, Singapore, Philippines, and Canada. No cases of SARS have been reported since 2004.

Transmission and risks to travellers

SARS is mainly spread by respiratory droplets produced when an infected person coughs or sneezes on someone in close proximity. The virus can also spread when a person touches a surface or object contaminated with infectious droplets. Airborne spread of the SARS virus might also be possible. The risk to travellers is predominantly from close contact with an infected person.

Illness

SARS is a viral respiratory illness that generally begins with a high fever. Possible associated symptoms include headache, malaise, and myalgia. Some people have mild respiratory symptoms at the outset. Rash and neurologic or gastrointestinal findings are generally absent, although 10–20% of patients have reported diarrhoea during the febrile prodrome. After 2–7 days, SARS patients may develop a dry cough or shortness of breath. Most patients develop pneumonia, and about 10%–20% of cases require mechanical ventilation because of hypoxia.

Prevention

Careful and frequent hand washing is most important for preventing infection. Travellers to areas reporting SARS cases should avoid settings where SARS is most likely to be transmitted, such as health-care facilities caring for SARS patients. The routine use of masks or other personal protective equipment while in public areas is not recommended.

Schistosomiasis ('bilharzia')

Organism

Caused by parasites (blood flukes) known as schistosomes. There are five species of schistosomes: *Schistosoma mansoni*, *S haematobium*, *S japonicum*, *S mekongi*, and *S intercalatum*. The first two species are the most prevalent. The parasite species differ in snail host, global distribution, egg morphology, preferred location of residence in the host, and pathophysiology.

Geographical distribution

At least 200 million people around the world are infected with schistosomiasis. *S mansoni* and *S haematobium* are distributed throughout Africa; *S haematobium* is also found in areas of the Middle East and *S mansoni* is present in some parts of South America and the Caribbean. *S japonicum* is found in Indonesia and parts of China and South-East Asia, *S mekongi* is found in Cambodia and Laos, and *S intercalatum* is found in parts of Central and West Africa (see Map 18).

Transmission and risk to travellers

Transmitted via skin contact with contaminated fresh water in which live certain types of snails that are essential to maintain the parasites' life cycle. Parasites leave the snail as cercariae and penetrate unbroken skin of individuals in contact with water.

In Australia, schistosomiasis occurs only as an imported infection in returned travellers or immigrants. The majority of travel-associated infections occur in people who have visited Africa, and the risk occurs in people who have contact with contaminated fresh waters, including rivers, streams and lakes. Areas that pose a particularly high risk include the Nile Valley, Lake Malawi, Lake Victoria, the Tigris and Euphrates river systems, and artificial lakes such as Lake Kariba in Zimbabwe and Lake Volta in Ghana. The risk of infection for travellers who swim in infected waters is of the order of 10%. Even brief exposure to contaminated water can result in infection.

Illness

Schistosomiasis infection is usually asymptomatic but can be associated with symptoms related either to acute infection or chronic complications.

1. **Acute presentations**: Travellers in particular may have a brisk immune response following exposure to the parasite, and within days of being infected may develop a rash or itchy skin where the larvae have entered the body (cercarial dermatitis), which resolves spontaneously. Within 1–2 months, fever, chills, cough and muscle ache may develop (Katayama fever). Eosinophilia is a common feature.

2. **Chronic complications**: The chance of developing chronic sequelae of schistosomiasis increases with high parasite and egg burdens. Complications include portal hypertension, cor pulmonale, intestinal schistosomiasis, fibrosis of the bladder and ureters with secondary obstruction, and calcification and malignancy within the urinary tract and bladder.

3. **Neurological complications**: Unlike most chronic complications of schistosomiasis, neurological sequelae can occur in individuals with minimal worm burden and therefore can be a problem for travellers. It is mainly because of the potential risk of neurological sequelae that screening and treatment is recommended for travellers who may have been exposed. Spinal schistosomiasis is most commonly seen and can be associated with paraplegia. Cerebral involvement with seizures, confusion and coma may also occur.

Prevention

There is no easy way to determine if water in endemic countries is contaminated with schistosomiasis, so travellers are advised to avoid swimming or wading in fresh water. Swimming in salt water (ocean or seas) or in chlorinated swimming pools is safe.

Ways to reduce the risk of infection include:

- Swim for short periods in flowing, rather than still, water.
- Avoid swimming during the early and late parts of the day.
- Vigorously rub oneself down with a towel immediately after leaving the water. Larvae die quickly on removal from water and cannot survive drying, so quick drying of exposed skin and clothing may offer some protection against infection.
- There is no vaccine available at present, and available drugs are not known to be effective as chemoprophylactic agents.

Strongyloidiasis

Organism

Strongyloides stercoralis.

Geographical distribution

Found mainly in tropical and subtropical areas, but cases also occur in temperate areas. It is more frequently found in rural areas or in institutional settings.

Transmission and risk to travellers

Infective filariform larvae, which are passed in faeces or develop in faecally contaminated soil, penetrate directly through the skin.

Illness

Infection is frequently asymptomatic. Clinical manifestations may include transient dermatitis following initial skin penetration, recurrent urticarial rash (larva currens), eosinophilic pneumonia, or gastrointestinal symptoms with abdominal pain and/or diarrhoea. Blood eosinophilia is generally present during the acute and chronic stages.

Unlike most helminths, which cannot replicate within a human host, strongyloides infection can result in an 'autoinfection' cycle, and the burden of adult worms can increase substantially without ongoing exposure. This autoinfection cycle also enables the organism to persist for decades and cause clinical manifestations long after the initial infection. In immunosuppressed patients, disseminated strongyloidiasis can occur, with abdominal pain, distension, shock, pulmonary and neurologic complications, and septicaemia. Disseminated infection is potentially fatal.

Exclusion of strongyloidiasis in those potentially exposed, and adequate treatment while a person is asymptomatic or mildly symptomatic, therefore has the potential to prevent life-threatening complications.

Prevention

- Be careful with personal hygiene.
- Use footwear in endemic areas and try to avoid direct contact of skin with soil.

Viral haemorrhagic fevers

Organism

Multiple viruses including arenaviruses (Junin, Machupo, Guanarito, Lassa); bunyaviruses (including Congo–Crimean, Rift Valley fever); flaviviruses (including yellow fever, dengue haemorrhagic fever); and filoviruses (Marburg and Ebola).

Geographical distribution

Multiple different viruses exist in different geographical areas. Most types exist in Africa, the Middle East or South America.

Transmission and risks to travellers

Most are spread by mosquitoes, ticks or rodents. Congo–Crimean, Lassa, Marburg and Ebola can also be spread from person to person. Apart from dengue (discussed separately above), most are very rare in travellers.

Illness

Often associated with fever, bleeding and shock. These should be considered in febrile travellers who have returned from an endemic area where active disease transmission has been reported. All have incubation periods of up to 2–3 weeks, so it may be possible to exclude viral haemorrhagic fever on epidemiological grounds alone.

Prevention

1. Avoid contact with associated vectors, including mosquito (precautions described above).
2. Yellow fever vaccine if travelling to endemic area

West Nile fever

Organism

West Nile virus is a flavivirus closely related to Japanese encephalitis, Kunjin, Murray Valley encephalitis, and St Louis encephalitis virus. The virus can infect humans, birds, mosquitoes, horses, and some other mammals.

Geographical distribution

It is commonly found in Africa, West Asia, and the Middle East. West Nile virus first appeared in North America in 1999, with encephalitis reported in

humans and horses. It is now permanently established in the western hemisphere.

Transmission and risks to travellers

West Nile virus is spread by the bite of an infected *Culex* mosquito. It does not spread from person to person or from animal to person. West Nile virus is amplified during periods of adult mosquito blood-feeding by continuous transmission between mosquito vectors and bird reservoir hosts. People, horses, and most other mammals are not known to develop infectious-level viraemias very often, and thus are probably 'dead-end' or incidental hosts.

In the temperate zone of the world (i.e. between latitudes 23.5° and 66.5° north and south), West Nile encephalitis cases occur primarily in the late summer or early autumn. In the southern climates where temperatures are milder, West Nile virus can be transmitted year-round.

Illness

Most West Nile virus infections are mild and often clinically unapparent. The incubation period ranges from 3 to 14 days. Approximately 20% of those infected develop a self-limiting mild febrile illness with headache and rash (West Nile fever).

Approximately 1 in 150 infections will result in severe neurological disease with encephalitis, meningitis ataxia, and extrapyramidal signs, optic neuritis, cranial nerve abnormalities, severe muscle weakness and flaccid paralysis, polyradiculitis, myelitis and seizures. The most significant risk factor for developing severe neurological disease is advanced age.

Prevention

- Reassure travellers that human illness from West Nile virus is rare, even in areas where the virus has been reported, and the chance of a mosquito bite leading to an illness is low.
- Advise travellers that they can further reduce the risk by protecting themselves from mosquito bites (as described above).

Key readings

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Chapter 6

Non-infectious Problems

Chapter outline

Five non-infectious problems of travel are set out in this chapter. Not all of them need to be discussed with every traveller, but travel-medicine practitioners need to be well acquainted with each.

Section 6.1, Fitness to fly, summarises some hazards of and the contraindications to air travel. This section is relevant for travellers with special needs. Section 6.2, Motion sickness, gives you the necessary information to advise travellers who seek help with this sometimes distressing problem. Jet lag (section 6.3) is a problem for many who cross several time zones, and is worth discussing with those involved in important activities where alertness and a high level of functioning are crucial within the first few days after arrival. Venous thrombosis (section 6.4) should be discussed with all travellers who may be at increased risk. Altitude sickness (section 6.5) should be discussed with all travellers going to places at altitudes higher than 2500 metres, and the table of altitudes of various destinations in this chapter can be useful.

6.1 Fitness to fly

Air travel

Each year, more than 1.5 billion people are estimated to travel by aircraft. While many of these people have medical conditions that pose no risk to themselves or to other passengers, there are some medical conditions that should preclude flying or that require pre-flight evaluation.

Most airlines have medical passenger policies to determine fitness to fly, in order to minimise the risk of disruption to other passengers and crew, the likelihood of aircraft diversion, and risks to the passenger's safety. They use a common passenger medical information form that asks details, from both patient and doctor, of diagnosis, prognosis, desired supplemental oxygen, and food and toilet requirements. The form is confidential but may be sent between airlines. It is the passenger's responsibility to contact the airline if any special arrangements need to be made.

Health effects of flying

Hypoxia

Reduced oxygen tension, pressure changes, and reduced space and mobility are the principal factors affecting the health of the air traveller.

As aircraft cabin altitude increases, there is a fall in the atmospheric pressure, together with a decrease in air oxygen tension, humidity, and temperature. At an altitude of 12 500 m the outside air pressure falls to 25% of sea level pressure, and the temperature falls to –60°C. In order to overcome the problem of barotrauma that would result at this altitude, airline cabins are pressurised. At cabin air pressure (equivalent to an altitude of 2000–2200 m), oxygen tension is approximately 70 mm Hg, resulting in a fall in haemoglobin saturation from a normal 98% at sea level to 92–94%. While this is easily tolerated by a healthy individual, those with cardiorespiratory disease or severe anaemia may experience marked hypoxia. This effect is exacerbated by alcohol.

In general, if the patient is able to walk 50 m and climb 15 stairs without symptoms, they will be able to fly without any special measures. Patients who do not meet these criteria require detailed evaluation, which may sometimes involve a high-altitude simulation test in a lung-function laboratory using a hypoxic gas mixture with a PO_2 equivalent to that in an aircraft cabin (see also chapter 7.7, Travellers with chronic lung disease).

Pressure changes

Falling cabin pressure during ascent results in expansion of air in closed cavities by approximately 30%, and corresponding compression on descent. During ascent or descent, air from the nasopharynx must enter the middle ear to maintain equilibrium. Eustachian tube dysfunction due to upper airway infection, otitis media or allergy such as hay fever, can prevent passive flow of air back into the middle ear cavity. This causes a relative increase in pressure on the outside of the tympanic membrane pushing it into the middle ear cavity and causing a sensation of fullness, a decrease in hearing acuity, and eventually pain. This barotrauma may result in tympanic membrane damage or, occasionally, persistent tinnitus or vestibular effects.

Patients should not fly if they are unable to clear their ears or the tympanic membrane does not move with a Valsalva manoeuvre. Performing active manoeuvres to open the Eustachian tube, such as swallowing, yawning and jaw movements, may assist in relieving the build up of pressure in the middle ear. Often, nasal decongestant sprays or oral decongestants taken 1 hour before descent can relieve Eustachian tube dysfunction.

Other conditions that may be affected by pressure changes include:

- air in the peritoneal cavity post-surgery (including laparoscopy) – generally wait 10 days. There should be a delay of 3 weeks after gut anastomosis or paralytic ileus, or significant gastrointestinal bleeding
- patients with a colostomy or ileostomy should be aware of the expansion of air in the gut (and bag) that occurs during ascent, and carry extra bags and other stoma equipment on board
- pneumothorax and pneumomediastinum
- plaster cast – air trapped in casts may cause limb compression, and splitting long limb plasters has been recommended pre-flight.

Flying is not recommended for at least 12 hours after scuba diving , and longer for prolonged or deep diving. It is not safe to fly immediately after a dive. The decreased pressure, even in a pressurised aircraft, can bring on an attack of the bends. Every diving agency has come up with different recommendations regarding flying after diving, but few of these have been tested. Guidelines for military and commercial divers will differ extensively from those of sport divers, due to conditions of diving and availability of treatment chambers. The following guidelines are recommended for recreational divers:

- <2 hours diving (no decompression) in the last 48 hours – wait 12 hours
- multi-day unlimited diving (no decompression) – wait 24 hours
- dives with decompression stops – wait 24–48 hours.

Reduced space and mobility

The prolonged period of immobility in confined space can be a risk for those individuals predisposed to develop deep vein thrombosis (DVT). See section 6.4, Venous thrombosis and travellers.

6.2 Motion sickness

Travel may be distressing and very uncomfortable for those severely affected by motion sickness. People may be restricted to the point of foregoing long trips or cancelling travel completely. Travel-medicine doctors should be sufficiently knowledgeable about this condition and know how it can be prevented and treated.

Table 6.1.1 Relative and absolute contraindications to air travel
This table is not exhaustive, and travellers with pre-existing health problems should also consult their usual doctor.

Medical condition	Recommendation
Respiratory disorders	
Active serious respiratory infections, particularly tuberculosis	Should not travel*
Pulmonary hypertension with or without cor pulmonale	Should not travel
Inadequate lung function as defined by one of the following parameters: • vital capacity or diffusion capacity <50% predicted • maximum voluntary ventilation <50% predicted • hypercapnia ($PaCO_2$ > 50 mm Hg) • hypoxaemia (PaO_2 < 55 mm Hg) on room air	Should not travel
On continuous oxygen therapy on the ground	Should not travel
Active bronchospasm, cyanosis at rest or during exercise	Adversely affected by hypoxia, should not travel
Thoracic surgery	Avoid travelling within 2 weeks
Pneumothorax or pneumomediastinum	Should not travel until completely radiologically resolved
Cardiovascular disorders	
Acute myocardial infarct	Avoid travelling within 3–4 weeks
Unstable angina	Should not travel
Uncontrolled heart failure or hypertension	Should not travel
Uncontrolled cardiac arrhythmia	Should not travel
Others	
Breathless after walking 50 m on the ground	Should not travel
Active thrombophlebitis or potential for pulmonary embolism	Precautions to prevent VTE
Deep vein thrombosis	No travel for 4 weeks; and then only if adequately anticoagulated
Stroke	Avoid travelling within 2 weeks
Gas introduced into body cavity	Avoid travelling within 10 days
Scuba diving (see above)	Should not travel for at least 12 hours after last dive
Anaemia with Hb < 75 g/L	Should not travel
Sickle cell disease with crisis within 10 days	Adversely affected by hypoxia. Should not travel
Otitis media, sinusitis	Avoid travelling within 10 days
Middle or inner ear surgery	Consult ENT surgeon. May need to wait for up to 2 months before flying
Pregnancy	Should not travel after 36 weeks for single uncomplicated pregnancy (see section 7.1)
Newborn and young infants	see chapter 7.2, Children

* The Department of Human Services Victoria recommends that a patient with pulmonary tuberculosis should have at least 2 weeks of effective anti-tuberculous treatment and 3 consecutive negative sputum smears (performed on separate days) before being allowed to fly (Tuberculosis management, prevention and control of tuberculosis: Guidelines for health care providers 2002–2005. Department of Health, Victoria; last updated 15 January 2008. <www.health.vic.gov.au/ideas/diseases/tb_mgmt_guide>. Accessed 20 May 2011). If they have drug resistant TB then they should have two negative sputum cultures before flying (Tuberculosis and Air Travel, 3rd edn, WHO 2008).

Motion sickness is triggered by movement or the visual suggestion of movement, and is usually associated with travel in cars, ships, planes, trains and buses. In some individuals, motion sickness can result from swimming or snorkelling in turbulent water. Constant exposure to motion over 3–4 days results in the development of a tolerance to motion sickness; however, this is generally short-lived once the motion stops.

It appears that a functioning vestibular system is essential for the development of motion sickness. Different types of real or perceived movement may trigger motion sickness. These include both linear and angular head acceleration. Blindness does not confer immunity to the condition.

Incidence and risk factors

Incidence varies depending on the magnitude of the stimulus and the susceptibility of the individual. It ranges from <1% on a large aircraft to 80% during whale-watching in a boat, and almost 100% on a rough sea voyage under evacuation conditions. Boat travel is most likely to cause motion sickness, followed by travel via air, car, and train.

Motion sickness is rare in those <2 years of age. The incidence is highest between the ages of 3 and 12, with a gradual decrease thereafter. It is least common in the elderly and is more common in females, especially during menstruation and pregnancy.

It is increased by visual stimuli, such as a moving horizon. The risk of developing motion sickness is also greatly increased by environmental factors such as poor ventilation, odours, fumes, smoke, and carbon monoxide.

Susceptibility to motion sickness can be exacerbated by fear or anxiety, other illnesses, poor health, and some medications. Personal susceptibility tends to be constant. Migraine sufferers are more likely to be sensitive to motion, and underlying conditions or medications that cause nausea may also increase the severity of motion sickness.

Symptoms and progression

The development of symptoms follows a sequence that varies with the intensity of the stimulus and the susceptibility of the individual.

The initial symptom is usually discomfort around the upper abdomen ('stomach awareness'), followed by nausea and increasing malaise. Concurrently, the face or area around the mouth becomes pale and the individual starts to sweat.

With rapid worsening of symptoms ('avalanche syndrome') there can be increased salivation, feelings of body warmth, a lightness of the head and often depression and apathy. Vomiting typically follows.

Additional frequent, more variable, symptoms include:

- belching and flatulence
- hyperventilation
- sighing and yawning
- headache
- tightness around the forehead or a 'buzzing' sensation
- drowsiness
- lethargy and somnolence
- panic or confusion.

Lethargy, fatigue, and drowsiness can persist after the stimulus stops and nausea lessens. This is referred to as the Sopite syndrome.

Prevention

General measures

- Minimise exposure. Be located in the middle of the plane/boat where movement is least. This has minimal impact on reducing symptoms in travellers with severe motion sickness.
- Minimise head and body movements. Assuming a semi-recumbent or recumbent position will ameliorate or prevent motion sickness by preventing exaggerated movement of the head and upper body.
- Restrict visual activity. This minimises conflicting visual stimuli that worsen motion sickness.
  - Fix vision on the horizon or some other stable external object.
  - Avoid fixation on a moving object.
  - Avoid fixation on close objects.
  - Avoid reading.
  - Close eyes, if below deck or in an enclosed cabin.
- Ensure good ventilation and remove noxious stimuli. This probably has little impact on reducing severity of symptoms, but may benefit some travellers.
- Reduce the magnitude of the motion stimulus. Avoid or minimise acceleration and deceleration, and turning or moving of the vehicle.
- Engage in distracting activity: be in control of the vehicle, perform mental activity.
- Avoid large meals, have frequent small food intakes, and avoid alcohol.

Medications

Drowsiness is common with all motion sickness medications. Symptoms are usually dose-related and it may be possible to strike a balance between efficacy and

adverse reactions. While these drugs reduce the symptoms of motion sickness they also interfere with the normal CNS response to conflicting vestibulo-visual inputs. The end result is that these medications slow adaptation to movement and consequently it may take the patient longer to adjust to motion than someone who does not take medications. The concomitant consumption of alcohol should be avoided with all medications listed below. All antihistamines are roughly equal in terms of their effectiveness, but some have a longer duration of action than others. Promethazine and dimenhydrinate are more sedating than cinnarzine. Metoclopramide (Maxolon) and phenothiazines (e.g. Stemetil), frequently used for vomiting or dizziness, are ineffective in preventing travel sickness.

None of the regimens provides total protection for everyone under all circumstances.

Dimenhydrinate

Dosage regimens include:

- Adults: 50–100 mg orally every 4–6 hours, to a maximum of 400 mg in 24 hours.
- Children 2–6 years of age: 15–25 mg orally every 6–8 hours, to a maximum of 75 mg in 24 hours.
- Children 6–12 years of age: 25–50 mg orally every 6–8 hours, to a maximum of 150 mg in 24 hours.
- Children >12 years of age: 50 mg orally every 4–6 hours, to a maximum of 300 mg in 24 hours.

This has long been considered one of the preventive treatments of choice for travellers, but is also one of the more sedating antihistamines. Compared to the scopolamine patch and promethazine, dimenhydrinate's major deficiency is its short half-life and the need for frequent administration. The most common adverse reactions are drowsiness and vertigo. In children there can be excitement. It should not be used in children <2 years of age, and it is not recommended for use in pregnancy.

Promethazine

Promethazine is available in two formulations:

- promethazine hydrochloride (Phenergan)
- promethazine theoclate (Avomine).

Dose:

- Adults: 25 mg orally 1–2 hours before travelling or at bedtime on the night before travelling, followed by a repeat dose in the morning, if necessary.
- Children >2 years of age: 0.25–0.5 mg/kg of body weight.

Promethazine has largely been used in situations of severe stimuli, and for treatment of established motion sickness.

Promethazine causes more drowsiness than most of the other standard agents. Its use is reported to result in significant decreases in performance scores, psychomotor function, information processing and alertness. However, results are conflicting and, under conditions of motion sickness, there may be less impairment than that attributable to the motion sickness itself.

It can be used in pregnancy, but should not be used in those <2 years of age.

Hyoscine hydrobromide (Kwells)

Dose:

- Adults: 0.3 mg tablet; 1–2 tablets (maximum four tablets/24 hours)
- Children 2–7 years of age: 1/4 tablet (maximum one tablet/24 hours)
- Children >7–18 years of age: 1/2 tablet (maximum two tablets/24 hours)

Hyoscine is probably the most effective drug for the prevention of travel sickness; it is also the most sedating. It is often the standard against which other medications have been compared. The major adverse reactions with hyoscine are similar to those discussed for the scopolamine patch (see below): dry mouth, drowsiness, blurring of vision.

It is contraindicated in pregnancy and children below 2 years of age.

Scopolamine patch

The scopolamine patch is the most effective of all the medications, but it is not available in Australia. It is available in the United Kingdom (Transcop) and in the United States (Transderm-Scop).

The scopolamine transdermal patch is applied to the skin behind the ear at least 8 hours prior to exposure to the stimulus, with replacement every 72 hours.

Its main advantages are its practical ease of administration and long duration of activity.

Commonly reported adverse effects include dry mouth (60%), drowsiness (less so than with antihistamines), and blurred vision (even without direct contact with the eyes). Visual problems may increase with continuous use. It can cause confusional states and/or visual hallucinations, particularly in elderly individuals. Rare instances of toxic psychosis have occurred. Some individuals have developed unilateral mydriasis from the patch.

The scopolamine patch can interact with sedatives (i.e. antihistamines, alcohol, antidepressants and anticholinergic-like belladonna alkaloids). Hands

should be washed after applying it to avoid inadvertent contact with the conjunctiva, with resultant pupillary dilation and blurred vision.

Use of the scopolamine patch is contraindicated in glaucoma, urinary retention or prostatic hypertrophy, children <12 years of age, and pregnancy. It should be avoided in the elderly.

Problems with its use include adverse reactions, which may outweigh the benefit when there are:

- minimal stimuli to induce motion sickness
- a long period before onset of activity
- inconsistent effects in different individuals and in the same individual at different times.

Cinnarizine

Dose (adult): 30 mg 1–2 hours before exposure and 15 mg every 6–8 hours thereafter. (This has been shown to be significantly more effective than placebo, and similar to scopolamine 0.3 mg every 6–8 hours.)

Cinnarizine is not available in Australia, but is available in Singapore and the United Kingdom. Many travellers can obtain this medicine from friends or while abroad. It is used by the armed forces overseas.

The major adverse reaction is drowsiness. Its use is not recommended in pregnancy, and no dosage recommendations are offered for age <5. For children aged 5–12 years, the adult dose is recommended.

Benzodiazepines

Dose:

- Oxazepam 15–30 mg as a single dose
- Temazepam 10–20 mg as a single dose.

These medications do not act on the central vestibular apparatus. However, they provide travellers with severe symptoms of motion sickness with a means to avoid the condition by sedation, and allow the traveller to sleep. These medications should be used with caution and not administered together with antihistamines or scopolamine. Alcohol should also be avoided, and they should not be used in children.

Recommendations

The following are recommendations for preventive use by travellers who do not need to drive or perform skilled tasks, using preparations available in Australia or easily obtained elsewhere. All medications are effective compared to a placebo, but none will work for all travellers. If one approach is not effective, or not

tolerated, another should be tried. Adverse reactions, prior experience and cost are factors in the choice of regimen.

For longer term travel many prefer the scopolamine patch, but it has several disadvantages. The recommendation to use alternatives (see below) as needed for mild stimuli is based on the observation that, with use of the patch, symptoms due to adverse reactions are more frequent than symptoms attributed to motion sickness when rough conditions are not encountered:

Short-term exposure (≤6 hours)

- Mild–moderate stimulus:
  - recommended – dimenhydrinate
  - alternative – promethazine.
- Intensive stimulus:
  - recommended – hyoscine, scopolamine or promethazine
  - alternative – dimenhydrinate or oxazepam.

Longer-term exposure (>6 hours)

- Mild stimulus:
  - recommended – dimenhydrinate as needed
  - alternatives – hyoscine, scopolamine, promethazine as needed.
- Moderate–intensive stimulus:
  - recommended – hyoscine, scopolamine or promethazine
  - alternatives – repeated doses of dimenhydrinate/promethazine or oxazepam.

Treatment of established symptoms

Options are more limited for treatment of established symptoms. Once vomiting has commenced, no oral regimen is likely to be effective. Intramuscular promethazine (25–50 mg) appears to be the most effective means of managing severe motion sickness, but few travellers will be able to administer intramuscular injections.

If exposure is likely to be prolonged, a scopolamine patch can also be applied, but this will not provide immediate benefit.

Acupressure, using a commercially available product applying pressure at a point above the wrist, has not been shown to be effective. Compounds like caffeine alone do not appear effective, but may counteract some of the drowsiness seen with common agents like the antihistamines.

Table 6.2.1 Drugs for prevention of motion sickness

Drug	Oral dose (mg)	Time interval before effective (h)	Duration of effectiveness (h)	Use in pregnancy	Use in children	Major adverse reactions	Severity of motion that drug is effective against
Cinnarizine	30	2–5	6–8	No	not <5 years	Drowsiness	Moderate to severe
Dimenhydrinate	50–100	1–2	6–8	No	not <2 years	Drowsiness, vertigo	Moderate
Promethazine	25	1.5–2	24–30	Yes	not <2 years	Extensive drowsiness, postural hypotension, extrapyramidal symptoms, delirium, neuroleptic malignant syndrome	Moderate–severe
Hyoscine hydrobromide (Kwells)	0.3–0.6	0.5–1	4–6	No	not <2 years	Dry mouth, drowsiness, blurred vision	Severe
Scopolamine patch (TTS)	1.5	6–8	72	No	No	Dry mouth, drowsiness, blurred vision, urinary retention, insomnia, psychosis	Moderate–severe

6.3 Jet lag

Jet lag refers to the various physical and psychological symptoms associated with crossing multiple time zones in a short period. These are due primarily to disturbance of the physiological circadian rhythm and sleep cycle. The physical and psychological effects of the activities before and during the flight contribute to these symptoms. As many as 94% of long-term travellers suffer from jet lag, and as many as 45% consider their symptoms to be troublesome.

Effects that may be expected due to the flight itself include tiredness, malaise and various aches and pains. These symptoms are exacerbated by fatigue, stress and dehydration. They seldom last more than a few hours after the end of the journey, and result from the duration of the flight rather than the number of time zones crossed.

In contrast, jet lag symptoms are common with time zone changes of 5 hours or more. The major problem is sleep disturbance, with periods of wakefulness occurring during the normal sleep pattern. This will result in some loss of sleep, with a consequent decrease in alertness, increase in irritability, alteration in performance efficiency and impaired manual and cognitive skills. Mood disturbance, anorexia and gastrointestinal symptoms are common.

While nearly all travellers will experience some symptoms with large time zone shifts, there is a considerable individual variation in severity and recovery time. Eastward travel is associated with difficulty falling asleep at bedtime and arising in the morning at the new destination. Westward travel is associated with early evening sleepiness and predawn awakening. Problems may increase with age. While most effects subside after a few days, a return to normal sleep patterns, body temperature and hormone levels may take up to 14 days. It takes approximately 1 day for each time zone crossed for the body to readjust completely to the new environment. It generally takes more time to reestablish circadian equilibrium with eastward as opposed to westward flights. In general, normal sleep returns within 2 days for westward travel and 5 days after eastward travel.

There is no panacea for the prevention and management of jet lag. However, there are some measures that can be adopted.

Preparation

Travellers crossing multiple time zones by air should be advised of the possibility and implications of jet lag. Reaction time is slowed for 2 days after a long flight. People should consider delaying important physical and intellectual activities (for example, competitive sports or critical negotiations) for 48 hours or more after arrival in a new time zone.

Travellers should be encouraged to be well rested and not sleep-deprived before the flight. They should adjust their activities, not be too hectic, and aim to have

2 good nights of sleep immediately prior to the flight. Short periods of sleep may be useful before a flight departing in the evening, or during very long flights when the entire period of wakefulness may be 16 hours or more. They should cut smoking before any flight. If possible, they should plan to arrive at usual bed time.

During the flight

Travellers should avoid overeating during flight. Adequate intake of fluids and limited alcohol intake on the flight reduces the possibility of dehydration. Agents like caffeine that promote alterness will interfere with normal sleep patterns and may potentiate the adverse effects of jet lag.

Wearing loose fitting clothes and shoes makes the trip more comfortable. Alternate tensing and relaxation of muscles or exercises involving only limited movement of the neck, back, arms or legs can be performed conveniently within the confines of the seat. Short naps during the flight may help to alleviate the symptoms of jet lag.

On arrival

Drinking plenty of fluids, avoiding eating heavily, avoiding drinking fluids containing alcohol or caffeine before bed, and gentle exercise, help reduce some of the symptoms of jet lag.

Travellers should attempt to adjust their cycle of sleeping, eating and activity to that of the destination. Outdoor light exposure at the destination may speed readjustment of the circadian rhythm and could reduce jet lag. Bright light in the early morning (5–11 am) causes a phase advance in body rhythms and helps to alleviate the severity of symptoms. After crossing up to nine time zones in a westward flight, self-adjustment to the new light–dark cycle is sufficient. In contrast, morning light should be avoided in eastbound travel. Evening light should be avoided after crossing nine time zones in either direction.

Travellers should try to get the same sleep per 24 hours while away as they would at home. Short naps of under 4 hours may help to compensate for sleep loss and improve alertness. Naps immediately prior to a duty period should be restricted to 45 minutes. Sleeping tablets are appropriate to treat temporary sleep difficulties and may reduce the time required to fall asleep, but their ability to keep insomniacs asleep is less certain. Before prescribing a drug, it is important to weigh up the benefits against any possible adverse effects, in particular the impairment of skills and decision-making ability. Short-acting benzodiazepines such as temazepam and lorazepam may be used to facilitate sleep for the first few nights in a new time zone.

Mild constipation during the first few days of travel is common. A mild aperient may be helpful.

Melatonin

Melatonin (N-acetyl-5-methoxy-tryptamine) is the principal substance secreted by the pineal gland, described 300 years ago by French philosopher René Descartes as the seat of the soul.

Although much about melatonin's role in humans is uncertain or unknown, there is increasing evidence that it has a role in the regulation of circadian rhythms, sleep, mood, tumour growth, ageing, and possibly reproduction. The circadian rhythm of melatonin secretion is endogenous. The day–night light cycle modifies the rhythm, and brief pulses of bright light cause abrupt suppression of melatonin production.

A number of studies have shown improvement in the symptoms of jet lag with exogenous melatonin (although the severity and duration of jet lag and the response to melatonin are highly variable between individuals). Melatonin has a hypnotic effect. It increases the speed of falling asleep, lengthens its duration, and improves the quality of sleep. It is unclear whether the benefit is primarily due to a hypnotic effect or resynchronisation of the circadian rhythm.

The timed administration of melatonin may help to alleviate jet lag. Melatonin given in the afternoon advances the body clock, while melatonin administered in the morning delays the circadian rhythm.

Availability

The availability of melatonin is limited in Australia; however, melatonin preparations are widely available in health food stores in some countries such as the United States. Although these preparations are almost certainly synthetic (as an estimated 1 million bovine pineal glands would be required to produce 10 mg of melatonin), most preparations are not produced under good, regulated manufacturing conditions and therefore their purity and quality is uncertain.

Available melatonin tablets generally contain 1–5 mg, and result in serum concentrations 10–100 times higher than usual night peak levels. Levels within the normal night range are achieved by doses of 0.1–0.3 mg.

Adverse effects

No serious side effects of melatonin are reported. Side-effects reported include mild sedation (8.3%), headache/migraine (1.7%), nausea (0.8%) and lightheadedness (0.8%). Concern has been expressed about driving or piloting aircraft after taking melatonin, as subjective sleepiness is increased. There has not been an adverse effect of 5 mg melatonin demonstrated on driving performance. However, caution should be advised when driving, flying aircraft or operating heavy machinery under the effects of melatonin.

Use

For those who suffer prolonged or severe jet lag, particularly in settings where a high level of functioning is demanded, and who travel frequently, melatonin can be very helpful. The lack of assurance regarding the quality and consistency of preparations remains a concern. It is likely that a range of preparations of assured quality will become available in the future.

The optimal dosage and timing are unclear. Available literature suggests 3–5 mg of melatonin should be taken at bedtime (local time) starting the first evening after arrival and continuing for the next 5 days. This dosage applies regardless of the direction of travel. For eastbound night flights, one dose of melatonin may be taken during the late afternoon on the day of travel to advance the biological clock and facilitate sleep during the flight. Additional doses of melatonin are not recommended for westbound flights.

Key readings

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6.4 Venous thrombosis and travellers

Background

Venous thromboembolism (VTE) is a serious medical condition with significant morbidity and mortality. It was first described in relation to air travel in 1954, and the popular phrase that has recently been used to describe it, 'economy class syndrome', was coined in 1997. It describes the development of lower limb venous thrombosis and secondary pulmonary embolism (PE) related to the effects of prolonged aircraft travel, especially in the more crowded environment of economy class. Of recent times it has received increasing amounts of publicity due to an increased media awareness of the condition, and the instigation of litigation against airlines following the development of VTE in airline passengers. It is not confined to economy class travel.

Possible predisposing factors

There are a number of theoretical reasons that suggest airline travellers would be predisposed to VTE. These include:

1. the compression of the popliteal vein against the plane seat in a sitting position combined with prolonged immobilisation likely leads to venous stasis

2. haemoconcentration due to the relative dehydration induced by insensitive water losses in the low humidity of the plane cabin, combined with a reduction in fluid intake and the diuretic effects of the often-consumed alcohol
3. the reduction in air-pressure and the relative hypoxia in a plane reduce fibrinolytic activity, and also increase the serum markers of coagulation activation, suggesting an increased likelihood of coagulopathy.

What are the risks?

The absolute risk of VTE related to air travel is low, with estimates of 0.34–0.4 cases for 10 000 people. Likewise the risk of acute non-fatal pulmonary embolism (PE) after air travel >12 hours or >10 000 km was no more than 1 in 200 000 passengers. This compares with an estimated annual risk of VTE in the general population of 1 in 1000 people.

Although there has been some conflicting data, most studies have shown an increased risk of VTE associated with air travel.

Sarvesaran in 1986 examined sudden deaths associated with commercial air travel at London's Heathrow airport over a three-year period. He noted that there was an increased incidence of VTE-related deaths in those dying during plane travel compared with those awaiting departure, and that 91% of these occurred on flights of between 12 and 18 hours duration. The LONFLIT studies looked prospectively at the incidence of deep vein thrombosis (DVT) within 24 hours of airline flights in economy class lasting >7 hours, and found a 3% incidence of DVT in those at risk of VTE, although no cases occurred in those without a predisposing condition to VTE (Cesarone 2002). A study of people arriving with PE at Charles de Gaulle airport in Paris showed that the risk of PE increased significantly with increasing preceding travel distances >2500 km and times >6 hours (Lapostelle 2001). More recently, an Australian study showed a four-fold increased risk of VTE in the 2 weeks following international travel (Kelman 2003).

In summary, there appears to be an increased risk of VTE associated with airline travel. However, this risk is likely to be small, and occurs largely in those with known risk factors for VTE (see Table 6.4.1) and in those undertaking long-haul travel (>6 hours or >2500 km).

Recommendations for prophylaxis

There are a number of general measures that can be instituted for all passengers to theoretically lower this possible risk. These include:

- regular movement around the cabin and leg-stretching exercises while sitting
- ensuring adequate leg room by avoiding the storage of hand luggage under the seat in front

- sitting in an aisle seat
- maintaining adequate hydration by the consumption of adequate water (1 glass every 2 hours) and avoiding alcohol before and during the flight
- avoiding the use of restrictive clothing.

For those who have conditions associated with a known increased risk of VTE, and therefore an even higher likelihood of airline travel-related VTE, there are a number of other prophylactic measures that can be instituted.

1. **Graduated compression stockings** worn from the feet to above the knees have been shown to reduce the incidence of DVT in people at increased risk of VTE during prolonged air travel, though with an increased risk of superficial thrombophlebitis. We therefore feel these should be recommended in all those with an underlying predisposition, unless there is arterial insufficiency that is a contraindication for using these stockings.

2. Some authorities recommend **aspirin** in a dose of 150–300 mg be taken a few hours prior to the flight for those at high risk. There is conflicting evidence regarding the effectiveness of aspirin in preventing VTE and the benefit obtained from taking aspirin is likely to be minimal.

3. **Low molecular weight heparin** is substantially more effective at preventing VTE than aspirin, and it has been shown to be effective in the setting of airline travel >10 hours. A single prophylactic dose of a low molecular weight heparin could be given immediately prior to travel for adults at moderate to high risk of VTE, in conjunction with compression stockings, and repeated if travel is longer than 24 hours. There is no evidence available to recommend its use in children.

   However, the use of low molecular weight heparin is not advised if there is a coexistent medical condition with a risk of bleeding, such as peptic ulcer or cerebral haemorrhage.

Key readings

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Table 6.4.1 Graduated risk for VTE in those with an underlying predisposition and additional prophylactic measures

Risk Level	Risk factors	Prophylaxis
High risk	Prior history VTE	Prophylactic dose of low molecular weight heparin
	Malignancy	Compression stockings
	Recent surgery, trauma or leg immobilisation	
	Inherited disorders of coagulation	
Moderate risk	Pregnancy and puerperium	Prophylactic dose of low molecular weight heparin
	Hormone therapy (e.g. HRT, OCP)	Compression stockings
	Haematological disorders (e.g. myeloproliferative disorders)	
	Recent myocardial infarction or heart failure	
Low risk	Chronic venous insufficiency	Compression stockings
	Obesity	
	Age >40 years	

6.5 Altitude sickness

An increasing number of travellers are visiting high-altitude regions (>1500 m) as part of their trip. The ease and rapidity with which travellers can now reach high-altitude destinations places many at risk of developing the symptoms of altitude sickness (AS). This is compounded by not allowing sufficient time for acclimatisation after arrival at such destinations (e.g. going on the Inca trail in South America). Altitude sickness is a preventable disease. Travellers to the Himalayas, Tibet, Nepal, the Andes, Mount Kilimanjaro, Mount Kenya, and the Rockies of Canada and the United States should be warned of this problem.

Altitude sickness is not just a problem for mountain climbers; they are often well informed of the dangers associated with such travel and know more about the issue than most travel-medicine doctors. It is the adventure travellers who are not so knowledgeable. They need to be well advised and educated about prevention, self-diagnosis and treatment of altitude sickness. Providing written material about AS will help travellers avoid and manage this condition. The

Table 6.5.1 Altitude and effects

Altitude	Effects
High altitude 1500–3500 m (4900–11 500 ft)	Decreased exercise performance and increased ventilation (lower arterial PCO_2) occur without major impairment in arterial oxygen transport, even though AS is common with abrupt ascent to >2500 m (8200 ft) At 2400 m (8000 ft) the PO_2 is 75% that of a standard atmosphere
Very high altitude 3500–5500 m (11 500–18 000 ft)	Maximum arterial oxygen saturation falls to <90% (PaO_2 <60 mmHg); marked hypoxaemia may occur during exercise and sleep
Extreme altitude >5500 m (18 000 ft)	Severe hypoxaemia and hypocapnia occur.

websites at the end of this chapter provide information from the High Altitude Medicine Guide; they go into more detail than we do in this chapter.

What is altitude sickness?

Altitude sickness is caused by the reduction in atmospheric pressure as elevation increases. Less oxygen reaches the muscles and brain, and the heart and lungs must work harder to compensate. The risk of developing symptoms increases with altitude and with the rate of ascent (see Table 6.5.1, Altitude and effects).

Acclimatisation refers to the process by which an individual adjusts physiologically to the hypoxia that results from the low oxygen concentrations at high altitude. It is a slow process, taking place over several days. Travellers who drive, ride or fly to high-altitude tourist sites in the Andes and Himalayas are more at risk than those who walk. Some travellers who ascend rapidly to heights >2500 m will have altitude-related illness during acclimatisation.

Susceptibility to AS varies greatly between individuals. Men, women and children are at equal risk. The risk is lower after age 50. Physical fitness provides no protection from altitude sickness. A past history of AS is the best predictor. Travellers with underlying cardiopulmonary disease or anaemia may have more severe hypoxaemia or cardiac ischaemia at higher altitudes.

Altitude sickness spans a spectrum of illness from mild to severe, from acute mountain sickness (AMS) on the mild end to high-altitude cerebral oedema (HACE) and high-altitude pulmonary oedema (HAPE) on the severe end. This division assists in predicting the likelihood of the traveller developing symptoms of AMS.

Incidence of altitude sickness

Altitude sickness is infrequent <2500 m. It occurs in 25% of travellers to the Rocky Mountains of Colorado who ascend to high altitudes of 1900–2950 m, and approximately 50% of adult tourists on the popular trekking routes in

Table 6.5.2 Altitudes of selected cities and mountains

	Height above sea level	
	m	**ft**
Cities		
Addis Ababa, Ethiopia	2408	7900
Arequipa, Peru	2304	7559
Asmara, Eritrea	2374	7789
Aspen, United States	2410–3417	7904–11 208
Banff, Canada	1397	4582
Bogotá, Colombia	2645	8393
Cochabamba, Bolivia	2550	8367
Cuzco, Peru	3225	10 600
Kathmandu, Nepal	1337	4388
La Paz, Bolivia	3658	12 000
Leh, India	3506	11 503
Lhasa, Tibet	3685	12 090
Mexico City, Mexico	2308	7572
Machu Pichu	1900	6232
Nairobi, Kenya	1820	5971
Potosi, Bolivia	3976	13 045
Quito, Ecuador	2879	9446
Toluca, Mexico	2680	8793
Zacatecas, Mexico	2446	8025
Mountains		
Annapurna	8078	26 496
Everest base camp	5150	16 900
Khunjerab Pass (Silk road)	4730	15 520
Mont Blanc	4807	15 771
Mt Everest	8848	29 028
Mt Kilimanjaro	5895	19 340
Mt Kenya	5199	17 058
West Yellowstone Mt, United States	2025	6644
Yosemite National Park, United States	1210	3970

Nepal. Several studies have found the incidence of AS to be 15–30% in Colorado skiers, 50% in climbers on Mount McKinley in Alaska, and 25–50% in trekkers to the base of Mount Everest. Direct arrival into La Paz (3658 m) will result in symptoms of AS in 25–35% of travellers. In general, the incidence of developing AS is 10% at an altitude of 2300 m, 40% at 3000 m and 70% in those undergoing rapid ascent to 4500 m. AS may develop in any journey >3500 m, especially when the person has not acclimatised for 1–2 days at an intermediate altitude. Of note, travellers can reach altitudes of 5400 m in Nepal and 6400 m in Tibet without requiring any technical climbing ability.

Normal symptoms at altitude

Certain physiologic changes occur in every person who goes to altitude:

- hyperventilation/dyspnoea on exertion (*not* dyspnoea at rest); shortness of breath with exertion is normal if the sensation of shortness of breath resolves rapidly with rest
- increased urination
- waking frequently at night
- periodic breathing at night: periods of hyperpnoea followed by apnoea (lasting up to 10–15 seconds). It may lessen slightly with acclimatisation, but does not resolve until descent. It becomes more pronounced with ascent, but is not a sign of altitude sickness.

Acute mountain sickness (AMS)

AMS comprises a variety of symptoms that represent the body not being acclimatised to its current altitude. Symptoms of AMS include:

- headache (not relieved by rehydration and mild analgesic)
- dizziness
- fatigue and weakness
- gastrointestinal upset: anorexia, nausea, vomiting
- general feeling of being unwell (often compared to the flu or a hangover)
- insomnia
- irritability.

AMS takes from a few hours to a few days to develop (usually during the first 8–24 hours at high altitude). In rare cases, AMS may be delayed by as long as 3 weeks. It is usually self-limited and resolves in 24–48 hours by resting at the same altitude, but it may progress to a more severe form. Therefore, symptoms of AMS are an important warning and should not be ignored. Travellers should be made aware that denial of AMS is common, and they should not regard a headache at altitude as 'normal'. As AMS progresses patients develop severe headache, vomiting, oliguria, worsening dyspnoea, and severe lassitude.

Assume that any illness (or poor performance) at altitude is altitude sickness until proven otherwise.

Severe altitude sickness

Severe AS may be fatal. It may develop from a benign AMS or may begin with little or no warning. There are two forms (these may occur independently, but they usually occur together):

1. HAPE (high altitude pulmonary oedema)
2. HACE (high altitude cerebral oedema).

HAPE often occurs on the second night after ascent to altitude. It is the most common cause of fatality due to high altitude. Up to 3% of travellers ascending to altitudes above 3000 m develop HAPE. It occurs in 1.6% of trekkers to Everest base camp (5150 m) and 3% of adults trekking in Peru at 3782 m. Early symptoms include:

- decreased exercise performance
- dry cough
- fatigue
- tachycardia
- tachypnoea.

These symptoms may progress to productive cough with frothy white or blood-stained sputum, dyspnoea and cyanosis.

HACE usually presents several days after onset of AMS. However, HACE can develop rapidly over as little as 12 hours of symptoms and death may occur within 24 hours of onset of AMS. It is very uncommon <3050 m. Rapid ascent to significant altitudes strongly predisposes to the development of HACE. The symptoms, which can progress to coma, include:

- truncal ataxia (the most sensitive early sign)
- impaired judgement
- inability to make decisions
- irrational behaviour
- confusion
- severe headache
- nausea
- vomiting
- severe lassitude
- drowsiness

- giddiness
- coma and death.

Warning signs for travellers

Travellers should suspect significant altitude sickness **in themselves** if they have:

- a headache and feel hungover
- shortness of breath (respiratory rate >20 per minute at rest)
- anorexia
- vomiting episodes
- ataxia (difficulty walking a straight line)
- unusual fatigue while walking.

Travellers should suspect significant altitude sickness **in their companions** who are:

- skipping meals
- exhibiting antisocial behaviour
- stumbling
- having difficulty with activity.

Prevention

The most effective way to avoid AMS is **gradual acclimatisation and slow ascent**. Climbers should be advised against strenuous over-exertion for the first few days at altitude. Exercise is equivalent to further ascent. Rest is an essential part of acclimatisation, and should be achieved at an altitude of 1500–2500 m for 2–4 days ('rest days') before ascending to a higher elevation. Acclimatisation also occurs during a slow gradual ascent.

The altitude at which the climber sleeps is the most important factor in slow ascent. Once above 2500 m, care should be taken not to increase sleeping altitude by more than 300 m per day, and to spend an extra 2 nights for each 1000 m gained. Even this rate of ascent may be too fast for some. In general, a climber is safe if he/she sticks to these simple rules, even if the traveller undertakes higher ascents during the day.

Those who fly to high altitude must be prepared to spend time acclimatising on arrival. During these 'rest days' the traveller can climb to much higher altitudes provided he/she returns to sleep at the same altitude as the previous night. **'Climb high, sleep low' is the key.** It is better to walk than to fly to any altitude >3000 m. While it is reasonable for healthy people up to the age of 70 years to fly to an altitude of 3500 m, symptoms of AMS are likely to occur. It is best for

Guidelines for the prevention of altitude sickness

- Ascend slowly.
- Climb high; sleep low.
  - Spend 1 night at altitude 1500–2000 m before sleeping at altitudes >2500 m.
  - At altitudes above 2500 m, sleep no more than 300 m above the starting altitude.
  - Allow 2 nights acclimatisation for every 1000 m gain in camp altitude starting at 3000 m.
- Avoid over-exertion.
- Drink extra fluids – increase the usual fluid intake by 1–2 litres per day.
- Eat a high carbohydrate diet.
- Avoid alcohol, sedatives and tranquillisers, tobacco and any other kind of smoke.
- Use prophylaxis (generally acetazolamide) if past history of altitude sickness, or abrupt forced ascent to >3000 m.
- Listen to your guide.

those aged >70 years with known cardiac or lung problems, especially if taking beta-blockers, to remain below altitudes of 2000 m.

Water loss increases during an active day in the dry, cold air at high altitude. Therefore, fluid intake should be increased (the climber may need as much as 4–7 L/day). A high carbohydrate diet (as opposed to high fat) increases respiratory quotient and improves efficiency of oxygen use at very high altitude. This reduces the symptoms of AMS by 30%. Smoking exacerbates hypoxia and should be avoided.

Drugs

Several drugs have been recommended for the prevention of AMS and HAPE. They can reduce the symptoms, but severe and even fatal AMS has occurred in people taking these drugs. In general, they are not recommended for travellers. It is much safer to rely on good planning and gradual ascent rather than medication.

Acetazolamide

Dose: 125 mg every 12 hours, beginning 24 hours before the ascent to altitude >2500 m, and continued for 3–5 days at the higher altitude (acetazolamide decreases the frequency of AMS by 30–50%).

Acetazolamide decreases susceptibility to AMS, reducing symptoms by speeding acclimatisation. It does this by inhibiting carbonic anhydrase in the kidneys and lungs, thus promoting excretion of bicarbonate and causing a slight metabolic acidosis (which encourages hyperventilation). It does not mask the

symptoms of AMS. It will not prevent AMS from worsening during ascent. Never ascend with symptoms of AMS.

Side-effects of acetazolamide are common, but they are mild and usually well tolerated. They include paraesthesiae, bowel disturbances, drowsiness, increased urine output, and an unpleasant change in the taste of beer and other carbonated drinks. Mild tingling of hands and feet is common and is not an indication to stop the use of acetazolamide.

Side-effects of acetazolamide may be mistaken for altitude sickness, and a trial of the drug at low altitude can help clarify this.

Individuals who are allergic to sulfonamides, those on high-dose aspirin therapy, or pregnant or breast-feeding women, should not take acetazolamide.

Indications for the use of acetazolamide are:

- flying to altitudes of ≥3000 m and staying there for >6 hours (for example, flying into Lhasa, Tibet or La Paz, Bolivia)
- past history of AMS
- a rapid gain in sleeping altitude (for example, moving camp by 1000 m in one day).

Dexamethasone

Dose: 4 mg every 6 hours, beginning day of the ascent, continued for 3 days at the higher altitude, then tapered over 5 days.

Dexamethasone is as effective as acetazolamide in preventing AMS. It can completely reverse the symptoms of AMS in a few hours, but it does not aid acclimatisation, and symptoms of AMS can occur after the abrupt discontinuation of the drug. Dexamethasone is generally recommended for treatment rather than prevention of AMS. Dexamethasone is superior to acetazolamide in treating AMS and HACE.

If there is no alternative (for example, allergy to sulfonamide) it is the best agent to use when rapid ascent to >3000 m is unavoidable.

Nifedipine

Nifedipine may be used to prevents HAPE in persons who are particularly susceptible to the condition. The adult dosage is 20 mg of extended release every 8–12 hours.

Salmeterol

The administration of salmeterol by a metered-dose inhaler is a relatively new addition to the drugs that are available to prevent HAPE. In a recent study

examining the preventive benefits of salmeterol in a group of mountaineers who previously experienced episodes of HAPE, it was found that when administered in a dose of 125 microgram 12 hourly commencing the day prior to ascent and continued for 2–4 days, salmeterol reduced the incidence of HAPE by more than 50%. The benefits of salmeterol are in preventing HAPE. It has not been tested against the development of the symptoms of AMS. Salmeterol should therefore be used in conjunction with acetazolamide in travellers who have had HAPE in the past or in those trekking to very high altitudes (>4000 m).

Sildenafil (Viagra), tadalafil (Cialis)

These two drugs, used mainly to treat erectile dysfunction in adult males, may prevent HAPE through their pulmonary vasodilatatory effects. Sildenafil 50 mg or tadalafil 10 mg twice a day can be given during ascent. They are also being studied for treatment of HAPE.

Spironolactone

Dose: 25 mg orally 4 times daily may be as effective as acetazolamide. Experience with spironolactone is, however, limited, and it should be used only in those intolerant of acetazolamide.

Treatment

For practical purposes, drugs and oxygen have only a minor part to play in the emergency treatment of AMS. A well-informed, non-health professional can be as effective as a doctor.

AMS

In AMS the rule is to remain at the same altitude until recovery. This often takes only 1 or 2 days.

Most cases of AMS will improve with rest, small meals, aspirin or paracetamol, and avoidance of alcohol. If necessary, descent of a few hundred metres is usually curative. Insomnia should not be treated with sleeping pills, as they tend to aggravate a low oxygen level during sleep.

Acetazolamide is useful in treating the headache and nausea associated with mild AMS and for disturbed sleep due to irregular breathing and breathlessness. It is administered in a dose of 250 mg every 8–12 hours (5 mg/kg/day in 2–3 divided doses). Treatment should be continued until symptoms of AMS resolve. Alternatively dexamethasone is also a suitable treatment option for AMS in travellers who are unable to take acetazolamide.

Severe AMS

The most effective immediate measure in those with severe AMS is descent or evacuation to a lower altitude. This should be insisted upon by all means

available and with no loss of time. Frequently a descent of 500–1000 m is sufficient to improve both HAPE and HACE. Descent becomes increasingly important as the severity of AMS increases.

The following warning signs indicate **an immediate descent is necessary**:

- severe headache not relieved by aspirin
- unsteadiness on one's feet, inability to sit upright or other unusual behaviour
- repeated vomiting and drowsiness
- shortness of breath at rest
- cyanosis ('blue' nails and lips)
- cough and white frothy sputum
- mild AMS that does not resolve in 2–3 days.

If descent or evacuation is impossible, oxygen should be given at a flow rate of 2–3 L/min (recommended but not of proven benefit). Hyperbaric therapy (Gamow bag) combined with oxygen is preferable if descent cannot be initiated immediately.

Dexamethasone 8 mg initially, then 4 mg every 6 hours orally, intravenously or intramuscularly for 1–3 days, and then tapered over 5 days, can be used for HACE.

People with severe headache and loss of balance can be improved enough with this drug to allow for safe descent, or to convert them from a stretcher case to being able to walk. Once the drug is started, the **person must not ascend any higher**. If, after ceasing the drug, there are no further symptoms for 24 hours, ascent may be continued, but this only applies to those with mild to moderate AMS.

Nifedipine can be used for HAPE. This is administered in a dose of 10 mg sublingually every 8 hours, or 20 mg slow-release capsule every 8–12 hours. Further ascent should not be made while taking the drug.

Treatment of severe AMS

Treatment of HACE (high-altitude cerebral oedema)

- Descend
- Oxygen
- Dexamethasone 8 mg stat, 4 mg 6 hourly
- +/– acetazolamide

Treatment of HAPE (high-altitude pulmonary oedema)

- Descend
- Oxygen
- Nifedipine 10–20 mg sublingually, then 20 mg oral 6 hourly
- No morphine or diuretics

The Golden Rules (from High Altitude Medicine Guide)

1. Any illness at altitude is altitude sickness until proven otherwise.
2. Never ascend with symptoms of AMS.
3. If you are getting worse (or have HACE or HAPE), go down at once.
4. Never leave someone with AMS alone.

Acetazolamide is an alternative of unproven benefit in moderate to severe AMS.

Drug treatment should never be used to avoid descent, or to enable further ascent, by a person with AMS.

Altitude sickness in children

The incidence of AMS is approximately the same as for adults. It is harder to recognise AMS in children, as those <5 years of age rarely report symptoms such as headache, nausea, fatigue, anorexia, dizziness and sleep disturbance. Lethargy, irritability, excessive crying and refusal to eat may be the only indication of AMS. It is best to assume the presence of AMS when a child becomes unwell at >2500 m and begin descent immediately.

It is unwise for children to go trekking if they have had a recent upper respiratory tract infection, as pulmonary oedema is prone to develop in this setting.

Drug treatment for AMS has not been well studied in children, but in life-threatening situations drugs effective in adults given in paediatric doses should be used. **The use of medicines for the prevention of AMS in children cannot be recommended.**

When cerebral oedema or severe AMS are suspected, oxygen and dexamethasone (0.15 mg/kg/dose 4 hourly) should be given in combination with immediate descent.

Prolonged exposure to high altitude should be avoided in infants aged <1 year because of the risk of subacute infantile mountain sickness, a condition characterised by pulmonary hypertension and consequent right heart failure.

Children <2 years should not sleep at altitude >2000 m; children aged 2–10 years should not sleep at altitude >3000 m.

Key readings

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Useful sources on the web

High Altitude Medicine Guide: Altitude Illness Clinical Guide For Physicians. Available from <www.high-altitude-medicine.com/AMS-medical.html>.

High Altitude Medicine Guide: All About Altitude Illness – good information for travellers. Available from <www.high-altitude-medicine.com/AMS.html>.

International Society for Mountain Medicine. Available from <www.ismmed.org/np_altitude_tutorial.htm>.

Chapter 7

Travellers with Special Needs

Chapter outline

Certain groups may be at increased risk or may face particular issues when travelling. This chapter provides information regarding a number of these groups.

7.1 The pregnant traveller

Travel during pregnancy poses particular problems that should be considered in advance so that safety and comfort can be maintained.

There are a number of infectious diseases that may pose a greater risk in pregnancy. These include malaria, hepatitis, influenza, travellers' diarrhoea, and parasitic infestations. Other issues include the risk of an obstetric mishap far from home and good medical care, and problems created by air travel.

The pregnant traveller should consult her obstetrician regarding her risk of travel. If there is a history of obstetric problems or the pregnancy is regarded in any way as posing higher than normal risk, the traveller might need to reconsider the need to travel.

Potential contraindications to travel

The following obstetric, medical or travel conditions may be contraindications to travel.

Obstetric risk factors

- history of miscarriage, ectopic pregnancy, premature labour, placental abnormalities, toxaemia, gestational diabetes, hypertension
- cervical incompetence
- current pregnancy – multiple gestation, threatened abortion or vaginal bleeding
- primigravida at ≥35 or ≤15 years of age

General medical risk factors

- history of thromboembolic disease
- valvular heart disease or congestive cardiac failure
- severe anaemia
- chronic medical problems requiring frequent medical consultations or interventions

Hazardous destinations for pregnancy

- areas where chloroquine-resistant falciparum malaria is endemic
- high altitudes
- high-risk areas for life-threatening food- or insect-borne infections
- areas where live virus vaccines are required or recommended

General advice

The safest time for a pregnant woman to travel is during the second trimester. Travel after 36 weeks gestation is not advised, and most airlines will not allow it. If possible, it is sensible for a pregnant woman to travel with a companion.

Obstetric problems should be anticipated. The family doctor and obstetrician may recommend specific medical contacts at the destination, and should provide a letter detailing the medical and obstetric history as well as progress of the current pregnancy. Medications and documentation should be carried rather than packed in checked luggage.

Air travel

Air travel in pregnancy is safe for those without obstetric or medical complications. However there are some risks that require consideration.

≤24 weeks gestation

- No restrictions unless complicating obstetric or medical risk factors exist.

24–36 weeks gestation

- No restrictions unless complicating obstetric or medical risk factors exist.
- Domestic travel is usually permitted until 36 weeks gestation, international travel until 32 weeks for multiple pregnancies and 35 weeks for single pregnancies, though this may vary between airlines.
- International travel may not be permitted by some airlines (check with airline when booking reservations).
- The pregnant traveller should carry a letter from her obstetrician.

≥36 weeks gestation

- Air travel is discouraged unless unavoidable.
- If travel is essential, a doctor's letter is required by all airlines.

Other considerations with air travel

- Most commercial aeroplanes are pressurised up to an altitude of 2440 metres above sea level. This confers a risk of hypoxia, especially if the pregnant traveller is anaemic.
- Pregnancy increases the risk of venous thromboembolism during long flights. Pregnant travellers should be advised about measures aimed at reducing this risk:
  - Frequent exercise of the legs and feet, including walking up and down from time to time.
  - Avoid dehydration by drinking plenty of fluid not containing alcohol or caffeine.
  - Compression stockings worn above the knee will further reduce the risk.

The fetus is more sensitive to the adverse effects of cosmic radiation than are older children and adults. Because of the uncertainty concerning the magnitude of the risk at low levels of exposure, radiation protection authorities recommend that the additional exposure to an unborn child be kept to a level that is similar to the variation in natural background radiation. This equates to about 200 hours of flying. At this level of exposure, no observable health effects are expected.

Activities

Certain activities may need to be curtailed or avoided. Examples include:

- water skiing
- scuba diving to depths greater than 18 metres
- climbing to high altitudes, particularly greater than 2500 metres.

Nausea and vomiting

The tendency to nausea and vomiting in early pregnancy may be aggravated by travel. In general, drugs given for motion sickness should be avoided during the first trimester, but metoclopramide is safe (category A).

Immunisation

There is no evidence that any vaccine, inactivated or live, poses a risk during pregnancy. (The only exception is smallpox vaccination, which has been shown to cause fetal malformation.) However, the safety of many vaccines during pregnancy, particularly live vaccines, has not been established.

All vaccines should be avoided during the first trimester because of the possibility of a febrile reaction and the potential associated teratogenicity. Live attenuated vaccines should be avoided throughout pregnancy because of the hypothetical risk of harm to the fetus should transmission occur. For the same reason, if possible, pregnancy should be avoided for 28 days after the administration of a live vaccine.

Routine immunisations

Diphtheria/tetanus/pertussis vaccines

Tetanus immunity is very important for women who may deliver overseas, and pertussis immunity is important for all young parents. Adequate data on dTpa vaccine (Boostrix, Boostrix-IPV) use during pregnancy are not available, but there is no reason to suspect that it is unsafe. ADT is safe and may be given.

Influenza vaccine

There is an increased risk for influenza-related complications during pregnancy. Influenza vaccine is recommended for all pregnant women who will be in the second or third trimester during the influenza season, including those in the first trimester at the time of vaccination.

Measles–mumps–rubella (MMR)

Rubella vaccine (either monovalent or as MMR) has been given to pregnant women (usually inadvertently) without harm to the fetus. However, it is contraindicated in pregnancy. Women who are known to be susceptible to measles should consider deferring travel to countries where measles is prevalent.

Polio vaccines

Paralytic disease occurs with greater frequency when polio infection occurs during pregnancy. Therefore, an unimmunised pregnant woman going to a highly endemic area should be vaccinated. Inactivated polio vaccine (IPV) is safe if given during pregnancy.

Varicella vaccine (VV)

Although there is no evidence that VV has any effect on the fetus, it is not recommended during pregnancy, and vaccinees should not become pregnant for 28 days after vaccination. A non-immune pregnant household contact is not a contraindication to vaccination with VV of a healthy child or adult in the same household.

Travel-specific immunisations

Yellow fever vaccine

Yellow fever vaccine has been given to a large number of pregnant women with no adverse outcomes. However, it is generally contraindicated during pregnancy. It may be given if exposure is unavoidable and risk considered high, although consideration should be given to deferring travel. If the vaccine is required primarily for statutory reasons, consider providing a waiver.

Hepatitis A vaccine

Hepatitis A vaccine should be given to pregnant women who are non-immune and travelling to an area of risk. Although data are limited, no adverse effects on the developing fetus are expected.

Hepatitis B vaccine

Hepatitis B vaccine should be given if there is risk of exposure (e.g. if working as a healthcare worker). It is safe in pregnancy.

Typhoid vaccines

Injectable typhoid Vi polysaccharide vaccine is recommended for pregnant women travelling to endemic countries where water quality and sanitation is poor. Attenuated live oral typhoid vaccine is not recommended during pregnancy, although there is no evidence of risk to the fetus with either vaccine.

Cholera vaccine

Cholera is rare in travellers, and there is inadequate information on the use of inactivated oral cholera vaccines during pregnancy. Vaccination is not recommended during pregnancy.

Meningococcal vaccines

Polysaccharide vaccine may be given safely to pregnant women who will be travelling to an area where meningococcal disease is epidemic. There are no data on the use of conjugated vaccines in pregnancy.

Japanese encephalitis (JE) vaccines

The inactivated vaccine is unlikely to pose a risk to the developing fetus, but there is inadequate information about its safety. JE virus infection during the first and second trimester is associated with miscarriage. Consideration should be given to deferring travel, but vaccination should be considered if the risk is considered to be very high.

Rabies vaccine

Cell culture rabies vaccines may be given during pregnancy for pre- or post-exposure prophylaxis.

Bacille Calmette-Guérin (BCG)

BCG is contraindicated in pregnancy.

Malaria

Malaria tends to be more frequent and severe in pregnancy. Pregnant women are at higher risk due to pregnancy-specific immunological factors that make them more susceptible to malaria infection, adhesion receptors in the placenta that lead to placental parasite sequestration, and a particular attraction to *Anopheles* mosquitoes. Pregnant women develop a higher level of parasitaemia, with an increased likelihood of cerebral malaria, anaemia, pulmonary oedema and hypoglycaemia. Sludging of placental red blood cells may cause abruption or premature labour. There is an increased risk of dehydration, seizures, splenic rupture, thrombocytopenia and death in a baby born to a woman with malaria.

Anti-mosquito measures are obviously important, and chemoprophylaxis is essential.

Mosquito avoidance

N,N-diethyl-3-methylbenzamide (DEET) is safe and has a low risk of accumulation in the fetus. Information regarding other repellents is limited. Insecticide-treated nets are also safe and effective during pregnancy.

Chemoprophylaxis

Chloroquine and **proguanil** are safe, although widespread resistance limits this option. The standard proguanil doses may be inadequate for pregnant women (see pages 290–1), and folic acid supplementation is recommended.

Mefloquine is the drug of choice for pregnant woman at risk of chloroquine-resistant falciparum malaria during the second or third trimester. There have been concerns about an increased risk of miscarriage associated with mefloquine use in the first trimester, but most evidence suggests that it is safe throughout pregnancy. WHO and CDC recommend its use in the first trimester if the risk of malaria is high and travel cannot be deferred. Consideration should be given to avoiding areas with high-risk for mefloquine-resistant malaria.

Doxycycline is contraindicated during pregnancy, in breastfeeding mothers and in children <8 years of age.

The safety of **atovaquone–proguanil (Malarone)** has not been established during pregnancy and is therefore not recommended.

Primaquine is contraindicated during pregnancy.

Treatment

If emergency self-treatment for malaria is required, **quinine** is preferred. The limited data available suggest that **artemisinins** are effective and unlikely to cause fetal loss or abnormalities, particularly when used in late pregnancy. However, no study has had adequate power to rule out rare serious adverse events, even in the second and third trimesters.

Medical help should be sought as soon as possible after emergency self-treatment.

Food- and water-borne illness

Pregnant women may be at an increased risk of travellers' diarrhoea, due to reduced gastric acid secretion and an increased intestinal transit time. In addition, the consequences of dehydration may be severe, and include miscarriage, premature labour and shock.

In addition to the usual recommendations regarding food and water, pregnant women should **avoid**:

- uncooked meat (toxoplasma)
- soft, ripened cheeses (listeria)
- dehydration
- iodine water treatment, as frequent use may cause fetal goitre
- loperamide (Imodium), as its safety has not been established in pregnancy (category B3), and diphenoxylate (Lomotil), due to respiratory depression of the newborn (category C).

Oral rehydration therapy is the mainstay of treatment. Antibiotics are only indicated if there are prominent constitutional symptoms, including fever, blood in the stools and/or severe diarrhoea. Prophylactic antibiotics are not recommended.

Antimicrobial agents for treatment of diarrhoea in pregnant women

- Erythromycin, cephalosporins, amoxicillin and other penicillins are safe.
- The fluoroquinolones (ciprofloxacin and norfloxacin) are category B3 drugs and are best avoided unless the severity of diarrhoea justifies their use.

- Tetracyclines are contraindicated.
- Azithromycin (B1) can be used in pregnancy if necessary.
- Trimethoprim/sulphamethoxazole (co-trimoxazole) is a category C drug. Sulfonamides may cause jaundice and haemolytic anaemia in neonates, and should therefore be avoided during the last month of pregnancy. Trimethoprim may interfere with folic acid metabolism and animal experiments have shown that administration of very high doses of trimethoprim during organ development may give rise to birth defects typical of folic acid antagonism. A trimethoprim/sulfonamide combination should be reserved for severe travellers' diarrhoea during pregnancy, but folic acid supplementation should be given.
- Tinidazole (B3) and metronidazole (B2) are contraindicated in the first trimester, and their safety is uncertain in later pregnancy. They should be avoided unless treatment is deemed necessary for severe giardiasis or invasive amoebiasis.
- Mebendazole (B3) is generally not recommended in pregnancy. Albendazole (D) is contraindicated during pregnancy and for one month prior to conception. Ivermectin (B3) has been inadvertently administered to many pregnant women without adverse effects on the pregnancy or the fetus, but unless there is a strong requirement for its use it should be avoided in pregnancy until its safety is further established.

Other infections

Hepatitis E (spread by contaminated food or drink) is particularly serious in pregnant women; the case fatality rate up to 20% has been described in pregnant women affected in their third trimester of pregnancy.

Pregnant women already prone to **thrush** should be aware of the increased risk in the tropics.

Childbirth

Access to good medical facilities may be important, particularly for women with previous obstetric problems or whose pregnancies are at higher than normal risk for any other reason. In some areas, blood for transfusion may not be screened for HIV or other blood-borne infections. If possible, childbirth should occur in close proximity to the best available obstetric services and the safest available blood supply.

Breastfeeding

This is highly desirable, especially where the risk of infectious diseases for the baby is increased.

Table 7.1.1 Immunisation during pregnancy

Vaccine	Indications for vaccination during pregnancy
Live attenuated virus vaccines	
Measles–mumps–rubella	Contraindicated
Varicella	Contraindicated
Yellow fever	Contraindicated, except if exposure is unavoidable
Inactivated virus vaccines	
Hepatitis A	Recommended if non-immune and travelling to area of risk
Hepatitis B	Recommended for those at high risk
Influenza	Recommended for pregnancy during influenza season
Japanese encephalitis	Recommended if risk very high and travel cannot be deferred
Poliomyelitis	Recommended for high-risk areas
Rabies	Recommended for pre- or post-exposure prophylaxis
Live bacterial vaccines	
Bacille Calmette-Guérin (BCG)	Contraindicated
Typhoid (Ty21a)	Contraindicated
Inactivated bacterial vaccines	
Cholera (rCTB)	Contraindicated
Diphtheria/tetanus/pertussis (dTpa, ADT)	Recommended for those who will be working in close contact with infants
Haemophilus influenzae type b (Hib)	Only recommended for those at high risk
Meningococcal ACWY conjugate	Not recommended
Meningococcal C conjugate (MenCCV)	Recommended for those at increased risk of meningococcal disease or possible exposure to serogroup C
Meningococcal polysaccharide (4vMenPV)	Recommended for those at increased risk of meningococcal disease or possible exposure to serogroup A, W135 or Y if not vaccinated with 4vMenPV in the past 3 years
13-valent pneumococcal conjugate (13vPCV)	Not recommended
23-valent pneumococcal polysaccharide (23vPPV)	Recommended for those at increased risk of invasive pneumococcal disease who have not received 23vPPV in the past 5 years (and provided they have not received two previous doses)
Typhoid Vi polysaccharide	Recommended for those travelling to endemic countries where water quality and sanitation is poor
Other	
Tetanus/diphtheria toxoid	Recommended
Immunoglobulins, pooled or hyperimmune	Recommended for exposure to: measles, hepatitis A, hepatitis B, rabies or Australian bat lyssavirus, varicella viruses and tetanus

Veltri JC, Osimitz TG, Bradford DC, Page BC. 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 1994; 32(1):1–16.

After delivery

A healthy newborn baby can travel at any time after birth. Exposure of healthy infants to 15% oxygen (similar to international in-flight conditions) may result in a proportion of infants developing arterial oxygen saturation levels of <80% for periods of 1 minute or more. This is not of clinical significance in healthy infants. Indeed, in the first few weeks of life, babies have relative protection against hypoxia from fetal haemoglobin (HbF), which is able to bind oxygen with greater affinity. However, babies with underlying lung or cardiac problems should not travel until they are assessed by a paediatrician.

Contraception

Women and men should be advised to take adequate supplies of contraception. In many countries, condoms, a particular brand of oral contraceptive pill or other contraceptive devices may be difficult to obtain or may be of unreliable quality.

Diarrhoea may reduce the absorption and effectiveness of the oral contraceptive pill (and other medications). Unexpected breakthrough bleeding may be an indication that the pill is no longer providing adequate contraception, and for the rest of that cycle an additional method of protection should be employed.

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7.2 Children

The pre-travel consultation is a good time to review and update children's routine immunisations.

It is becoming increasingly common for families with young children to travel overseas to exotic locations. Travelling with children poses some challenges but

can also be very rewarding. Children encounter the same problems as adults, but don't always get appropriate pre-travel advice. There are some issues that are more complex to deal with in children. Young children may not be fully immunised with the routine schedule vaccines. The use of certain vaccines or drugs that are first line in adults may be contraindicated in children.

Rather than unusual tropical diseases, travel-related illness in children is more likely to be due to common problems such as trauma, skin and respiratory tract infections, and diarrhoea. Malaria and tuberculosis (TB) are important exceptions as both tend to be more frequent and severe than in adults.

Children become unwell and dehydrated more quickly than adults, although, fortunately, they tend to recover more quickly once appropriate treatment is instituted. Parents should be encouraged to seek early medical attention should illness arise in their child.

Children may be more susceptible than adults to variations in temperature. Excessive sun exposure should be avoided, sunscreen should be applied, and adequate fluid intake maintained. Appropriate clothing should be packed. Items of regular use (e.g. nappies, formula, etc.) may not be available in areas of travel, and adequate supplies need to be packed or alternatives planned for.

Parents should be encouraged to discuss travel plans and details of the destinations with their children to prepare them as best they can. Nonetheless, children may become confused, anxious or irritable during travel. Taking familiar personal items or favourite foods may be helpful.

Immunisations

Routine immunisations

Many of the diseases for which routine immunisations are given are rarely seen in Australia. However, some remain prevalent in developing countries; examples include measles in India and polio in Pakistan. Newer multivalent and conjugate vaccines may not be available in some of these countries, or may not be included in their national vaccination programs. It is worthwhile ensuring that a child's immunisation schedule is up to date at the time of travel.

Almost all of the routine vaccines can be given earlier and more frequently than the schedule recommends. The vaccines usually given at 2 months of age can be given from 6 weeks, and subsequent doses can be given 4 weeks apart. This means that the '6-month shots' could potentially be given by 14 weeks of age. An accelerated schedule may be of particular benefit to an infant being taken overseas for several months in their first year of life. The lower age limit and minimum interval between doses are listed in Table 7.2.1.

Table 7.2.1 Lower age limits and schedules for common vaccines

Vaccine	Lower age limit	Minimum interval between dose 1 and 2 (weeks)	Minimum interval between dose 2 and 3 (weeks)	Minimum interval between dose 3 and 4 (weeks)
Diphtheria–tetanus–pertussis vaccines	6 weeks	4	4	264
Injectable polio	0	4	4	4
Haemophilus influenzae type b (Hib) (PRP-OMP)	6 weeks	4	52	
Haemophilus influenzae type b (Hib) (PRP-T)	6 weeks	4	4	52
Hepatitis B	0	4	8	8
13vPCV	6 weeks	4	4	
Rotavirus (Rotarix)	6 weeks	4		
Rotavirus (RotaTeq)	6 weeks	4	4	
MMR	9 months	4		
MenCCV	6 weeks	8	8	
Varicella (Varilrix)	9 months	4		
Varicella (Varivax)	12 months	4		

Notes

- **Injectable polio vaccine**: If the third dose of IPV is given after 4 years of age, a fourth dose is not required. However, if using a combination vaccine, it is acceptable to receive a fourth dose.
- **Measles–mumps–rubella vaccine**: Measles is still common in many countries, and travel in densely populated areas may favour transmission. MMR may be given from 9 months of age. Children given MMR at <12 months of age should receive a booster 3 months later.
- **Hepatitis B vaccine**: Regardless of travel, all children should be immunised against hepatitis B, as infection at an early age carries a higher risk of chronic infection. Infection most often occurs by social contact with other children and cannot be effectively prevented by any means other than vaccination. If the first dose is given at birth or within 7 days of birth, then three subsequent doses should be given; otherwise two subsequent doses.
- **13-valent pneumococcal conjugate vaccine (13vPCV)**: The incidence of invasive pneumococcal disease is higher in less-developed countries than in Australia. The 13vPCV is the preferred pneumococcal vaccine for children under 5 years of age. It should be offered to all children aged between 3 months and 2 years, and to those with underlying medical conditions under the age of 5 years. The polysaccharide vaccine may be offered in certain circumstances (see section 2.11).
- **Meningococcal C conjugate vaccine (MenCCV)**: If two doses of MenCCV are given before 12 months of age, a booster dose should be given at 12 months of age.
- **Varicella vaccine**: If a child receives varicella vaccine at <12 months of age, a further dose should be given at 18 months of age. Children over the age of 12 years should receive two doses, 4–8 weeks apart.

Travel-specific immunisation

- **Yellow fever vaccine** should be given to children aged >9 months travelling in areas of South America and Africa where yellow fever is endemic, or to countries where immunisation is required (see chapter 2.19). It should not be given to children younger than 6 months due to the risk of vaccine-associated encephalitis.
- **Typhoid vaccine**:

Table 7.2.2 Vaccine schedule

Vaccine	Age routinely given	Accelerated schedule for travel
DTPa	2, 4, and 6 months + 4 years	6, 10 and 14 weeks + 4 years
Polio	2, 4, and 6 months + 4 years	Birth, 1 and 2 months +/- 3 months + 4 years
Hib	2, 4, and 6 months + 12 months	6 weeks, 10 weeks, 14 weeks + 12 months
MMR	12 months + 4 years	9 months + 4 years
Hepatitis B	2, 4 months and 6 or 12 months	Birth, 1 and 2 months, followed by a fourth dose 6–12 months later
13vPCV	2, 4, and 6 months	6, 10 and 14 weeks

  - **Injectable killed Vi typhoid vaccine** has been approved in Australia for use in children aged 2 years and over. Only 1 dose is required and side effects are minimal (see discussion of typhoid vaccine in children in chapter 2.17).
  - **The oral live vaccine** is as effective as the injectable one, has few side-effects, provides a longer period of protection, and is safe in children over the age of 1 year, although AIH and the manufacturers do not recommend it for children younger than 6 years. The factor limiting its use in children is their ability to swallow the capsules.

- **Hepatitis A (HA)**: The vaccine is safe, effective and long-lasting. The lower approved age limit for the monovalent vaccines is 1 year for Vaqta and 2 years for Avaxim and Havrix. As in adults, a single dose is given, followed by a booster 6–12 months later. While it is arguable that HA immunisation could be omitted for children <5 years undertaking short-term travel (<2 weeks at risk), particularly once-off, we feel the ongoing benefits of immunisation warrant use of the vaccine for children aged 12 months and older. However some parents have chosen not to have the vaccine for their young children in order to avoid two injections (initial shot and the booster). See discussion of use of this vaccine in children in chapter 2.4, Hepatitis A.
- **Combined HA/typhoid vaccine**: The individual hepatitis A and typhoid components of Vivaxim are the same as those in Avaxim and Typhim respectively. The individual vaccines are licensed for use from 2 years of age, although Vivaxim is only licensed for use in those over 16 years of age. We have been prescribing Vivaxim to children from 2 years of age (off label) for many years; safety and efficacy appear to be the same as for the individual vaccines. The whole volume (1.0 mL) must be given.
- **Polysaccharide meningococcal vaccine** covering serotypes A, C, W135 and Y is indicated for children travelling to highly endemic areas, particularly Sub-Saharan Africa and parts of the Middle East. The vaccine is not immunogenic against serogroup A in children <3 months of age or against serogroup C in children <18 months of age. Children under 2 years should

receive at least one dose (and a second dose 3 months later if there is a continuing risk of infection). Children immunised under 4 years of age should receive a booster after 3 years if they remain at risk. The Australian immunisation schedule includes one dose of meningococcal group C conjugate vaccine (MenCCV) at 12 months of age, but this vaccine does not provide immunity against serotypes other than C. A quadrivalent (A, C, W135 and Y) conjugate vaccine is licensed in the United States.

- Two conjugate meningococcal vaccines, Menveo (Novartis) and Menactra (Sanofi Pasteur), covering serotypes A, C, W135 and Y are now available in Australia, and should be used in preference to the polysaccharide vaccine where possible. Menactra is approved in Australia for use >2 years of age, and Menveo from 11 years of age. There are data confirming the safety and immunogenicity of Menveo down to 2 months of age (see chapter 2.9).
- **Rabies vaccine** is indicated for children of any age staying for prolonged periods in endemic areas, particularly where rabies immunoglobulin and vaccine are difficult to obtain. Children should be discouraged from any contact with unknown animals. Vaccination is more important in children than in adults as they:
  - are attracted to animals and are more likely to try to pat, play with or feed them
  - may not reliably report a minor animal bite
  - are more likely to suffer animal bites that are severe and multiple, or involve the upper limbs, head and neck.
- **Japanese encephalitis vaccine, JESPECT (IXIARO in US and Europe; IC51, Intercell)**, is not licensed for individuals below 18 years of age. It cannot be recommended for children until further data regarding safety and efficacy are available. In the meantime, families must be reminded to employ mosquito avoidance measures.
- **IMOJEV (JE Chimerivax, JE-CV, Sanofi Pasteur)** is a live attenuated yellow fever JE chimeric viral vaccine registered for use in children from the age of 12 months. At time of writing, it is not yet available.
- **BCG vaccine** is recommended for children <5 years who are expected to stay for more than a few weeks in areas with a high prevalence of TB (this includes most developing countries). The protective efficacy of BCG is only 50% overall, but it is approximately 80% protective against disseminated TB, tuberculous meningitis, and death from TB, which are more common in young children.

  Prior tuberculin skin testing is only indicated if there is deemed to be the possibility of previous exposure to TB. The dose of BCG for infants <12 months of age is 0.05 mL given intradermally, and 0.1 mL for children aged 12 months and over.

Table 7.2.3 Lower age limit for use of vaccines

Vaccine	Minimum age for first dose
BCG	0
Cholera	2 years
DTP	6 weeks
Poliomyelitis (IPV)	0
Hepatitis A	12 months
Hepatitis B	0
Hib (PRP-OMP)	6 weeks
Influenza	6 months
Japanese encephalitis vaccine (JESPECT)	18 years
Japanese encephalitis vaccine (IMOJEV)	12 months
Meningococcal C conjugate MenCCV	6 weeks
Meningococcal conjugate	2 months*
Meningococcal polysaccharide ACW135Y	2 years
MMR	9 months
Pneumococcal (13vPCV)	6 weeks
Rabies	0
Rotavirus	6 weeks
Typhoid (injectable)	2 years
Typhoid (oral)	1 year
Varicella (Varilrix)	9 months
Varicella (Varivax)	12 months
Yellow fever	9 months

* See text for further detail

- **Influenza vaccine**: Influenza is one of the most common travel-acquired vaccine-preventable illnesses. Although it is not fatal in most children, influenza infection can cause significant disruption to a family's travel plans. Vaccination should therefore be considered for all children >6 months of age travelling to areas during influenza season. It is especially important in children with underlying chronic lung disease.
- **Cholera vaccine**: The risk of cholera is extremely low for most travellers. The vaccine is only recommended if travel is to an area with a known outbreak. The oral live-attenuated vaccine (Dukoral) can be given to children >2 years.

Travellers' diarrhoea

Children are more likely to acquire travellers' diarrhoea than adults; they are immunologically inexperienced and have a higher gastric pH and a more rapid

gastric emptying time, resulting in decreased killing of ingested bacteria. In addition, they are more likely to place potentially contaminated hands or objects in their mouths, and are less selective in the foods they eat. Furthermore, if they develop diarrhoea they are more susceptible to dehydration. Prevention involves eating and drinking safely, regular handwashing, especially after toileting and before eating, and cleaning of toys. Breast-fed infants are at substantially less risk of food or water-borne infections.

Fluids and food

For **mild diarrhoea**, give extra fluids such as water, oral rehydration solution (ORS) or dilutions of drinks as follows:

- cordials (not low-calorie) – 1 part to 16 parts water (aiming for a final glucose concentration of approximately 2%)
- lemonade (not low-calorie, and does not need to be flat) – 1 part to 6 parts water
- fruit juice (not concentrated) – 1 part to 4 parts water
- sugar water – 1 level teaspoon (5 mL) of table sugar in 120 mL water.

If the child is hungry give a normal diet.

For **severe diarrhoea**, give 1 cup of ORS for every watery stool. There are many commercial ORS preparations around the world. Such solutions should ideally contain approximately 1.6% glucose and 60 mmol/L of sodium. Solutions widely available in Australia are Gastrolyte and Hydralyte. Adults travelling with children should carry a supply of ORS sachets.

Although commercially prepared ORS solutions are preferred, homemade ORS solutions are an alternative. Using a 5 mL teaspoon, 8 level teaspoons of table sugar and half a level teaspoon of salt can be added to 1 litre of water. Taste is not a reliable way of avoiding the addition of too much salt.

The most reliable signs of dehydration are weight loss and a fall in urine output. A dehydrated child should be given as much ORS as he/she will drink. A child who vomits will retain some ORS if given frequent small sips.

Feeding, particularly breast-feeding, should be continued. Solids should be stopped for no longer than 24 hours and preferably not at all.

When to seek help

Medical help should be sought if:

- there is blood in the stool
- a high fever is present
- diarrhoea persists for more than 3 days in a child or 1 day in a baby
- there is significant dehydration and an inability to tolerate oral fluids.

Medications

Medications are rarely necessary to treat diarrhoea in children. Most medications used by adults are inappropriate for children. The emphasis in management should be on fluid and electrolyte replacement and continued nutrition.

Antimotility and antinausea drugs

Antimotility drugs, e.g. loperamide (Imodium) and diphenoxylate (Lomotil), should not be used in children <6 years of age. Antiemetics, e.g. metoclopramide (Maxolon) or prochlorperazine (Stemetil), should be avoided in children <2 years of age, but Ondansetron (Zofran) may be used in infants >6 months of age. Ondansetron is available as a wafer, which may be easier to administer than a tablet. There is an increased propensity for side-effects with these medications. Paralytic ileus, toxic megacolon and bacteraemia have been reported in young children with infectious diarrhoea who have been inappropriately treated with antimotility agents, and dystonic reactions caused by antiemetics are more commonly seen in children.

Antibiotics

Antibiotics may be indicated for travellers' diarrhoea if the symptoms are severe or protracted. Chemoprophylaxis to prevent travellers' diarrhoea is not recommended for children.

Ciprofloxacin (10 mg/kg twice daily) or **norfloxacin** (10 mg/kg twice daily) can be used for severe or dysenteric disease. There are increasing rates of quinolone resistance, particularly in South-East Asia. No quinolone suspension is available. There are considerable data demonstrating the safety of fluoroquinolones in children. Previous concerns relating to their effects on cartilage have not been substantiated in more recent studies.

Azithromycin (15 mg/kg daily for 3 days is effective against most causes of severe diarrhoea including quinolone-resistant *Campylobacter*. A paediatric formulation is available.

Co-trimoxazole (trimethroprim/sulfamethoxazole) is no longer used as empiric treatment for travellers' diarrhoea, as the rates of resistance are high in all developing countries.

Doxycycline (2 mg/kg daily) is contraindicated under the age of 8.

Malaria

Young children are at increased risk of severe falciparum malaria, and death may occur within 24 hours of the onset of symptoms. Chemoprophylaxis should be offered to children travelling to areas where malaria transmission is high. However, there are lower age/weight limits for each of the most commonly used drugs. None of them is available as a suspension in Australia. It may be unwise

for young infants to travel to areas with high rates of resistant malaria, as there may not be an appropriate chemoprophylactic agent.

The risk of malaria (and other insect-borne diseases) can be substantially reduced by minimising mosquito exposure, particularly at night. Repellents containing N,N-diethylmetatoluamide (DEET) should be applied. Preparations containing >30% DEET should be avoided, and repellent should be applied sparingly at recommended intervals and washed off before going to bed. There have been numerous case reports of toxicity associated with DEET in children. However, these have mostly been poorly documented, and in many, >30% DEET was used and applied excessively. A retrospective study of 9086 reports of DEET toxicity showed that children were no more likely to develop adverse affects than adults, two-thirds of those exposed had no adverse effects, and 99% had no long-term sequelae. (See discussion of DEET in Chapter 3, Malaria prevention.)

If a child (or adult) becomes unwell with malaria, early diagnosis and treatment may save lives. In a febrile young child who is in or has recently visited a malaria endemic area, medical advice should be sought within 24 hours of the onset of fever. Emergency self-treatment has an important role for those in remote areas.

Antimalarial drugs

- **Chloroquine**, **proguanil** and **quinine** can safely be given to children of all ages. Chloroquine tablets can be given with honey or jam in an attempt to disguise the very bitter taste.
- **Mefloquine** tends to be tolerated better by children than adults. It can be given to children >5 kg. If vomiting occurs within 30 minutes of giving the medication it should be repeated. Mefloquine also has a very bitter taste, which can be disguised by giving it with something sweet such as jam. Tablets are not scored, so a tablet cutter may be necessary.
- **Atovaquone–proguanil (Malarone)** is not recommended for prophylaxis in children who weigh less than 5 kg. It is recommended for prophylaxis in children who weigh more than 10 kg. There are limited data in children who weigh less than 10 kg. It is given for prophylaxis in infants of more than 5 kg body weight in Belgium, Canada, France and the United States; but it is not recommended by WHO and UK authorities, nor the Australian Therapeutic Guidelines Antibiotic, version 14, 2010. We are prepared to use (and have done so for several years) atovaquone–proguanil for prophylaxis in children who weigh more than 5 kg. Paediatric tablets are available, and can be given to children >5 kg in weight.
- **Doxycycline** is contraindicated for children under 8 years of age (and mothers who are breast-feeding) because it affects growing bones and teeth.

Each of these drugs is excreted in breast milk, but will not protect the breastfed infant.

Dosage of chloroquine

Prophylactic dose: 5 mg/kg base once/week, up to a maximum of 300 mg base/week.

Age (year)	Weight (kg)	Fraction of tablet
<1	<10	1/4
1–4	10–19	1/4
5–8	20–30	1/2
9–15	31–45	3/4
>15	>45	Adult (300 mg)

Dosage of proguanil

Prophylactic dose: 3 mg/kg daily up to a maximum of 200 mg daily.

Age (year)	Dose
<1 year	25 mg/day
1–3 years	50 mg/day
4–6 years	75 mg/day
7–11 years	100 mg/day
12–16 years	150 mg/day
>16 years	200 mg/day

Dosage of mefloquine

Body weight (kg)	Dose	Dosage regimen
5–15	62.5 mg	1/4 tablet weekly
16–30	125 mg	1/2 tablet weekly
31–45	187.5 mg	3/4 tablet weekly
>45 kg	250 mg	1 tablet weekly

Dosage of atovaquone–proguanil (Malarone)

Body weight (kg)	Dose	Dosage regimen
5–20*	62.5 mg/25 mg	1 paediatric tablet daily
21–30	125 mg/50 mg	2 paediatric tablets daily
31–40	187.5 mg/75 mg	3 paediatric tablets daily
> 40	250 mg/100 mg	1 adult tablet daily

* Paediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride.

There are limited data on dosage for infants weighing <10 kg. The CDC recommend the following doses in infants weighing <20 kg:

Body weight (kg)	Dose	Dosage regimen
5–8	31.25 mg/12.5 mg	1/2 paediatric tablet daily
9–10	46.875 mg/18.75 mg	3/4 paediatric tablet daily
10–20	62.5 mg/25 mg	1 paediatric tablet daily

We have been using 62.5 mg/25 mg (1 paediatric tablet) daily for children weighing 5–20 kg; this is far more convenient for the parents.

Dosage of doxycycline

Body weight (kg)	Dose	Dosage regimen
25–35	50 mg	1/2 tablet daily
36–50	75 mg	3/4 tablet daily
>50	100 mg	1 tablet daily

Overdose of antimalarial drugs, even chloroquine, can be fatal. Store medication in child-proof containers out of reach of children.

Special considerations

Air travel

Exposure of healthy infants to 15% oxygen (similar to international in-flight conditions) may result in a proportion of infants developing arterial oxygen saturation levels of <80%. Therefore, babies with underlying lung or cardiac problems should not travel without prior consultation with a paediatrician (see p. 280).

It is also common for children to develop ear pain during the plane's descent, due to a build-up in pressure in their middle ear. Medications are not helpful, but techniques such as feeding, drinking from a cup or chewing gum during descent can help. Children can also be taught to yawn or blow their nose with the mouth closed in an attempt to equalise the pressure in the middle ear.

Children may find it very difficult to settle on a long flight, and this may be distressing to them, their parents, and others. Sedation may assist them to relax and fall asleep. Chloral hydrate has been well studied in children, and is safe and effective. It is available as a suspension and has a wide dosing range. Doses as low as 8 mg/kg can be given and repeated during the trip if required (up to 50 mg/kg), or up to 50 mg/kg can be given as a single hypnotic dose. Adverse effects include gastric irritation and vomiting in 5%, which can be

reduced by diluting with water or milk. Importantly, paradoxical agitation occurs in only 1–2%, compared with up to 15% for antihistamines such as Promethazine (Phenergan).

Accidents

In unfamiliar and changing environments, children are especially susceptible to accidents. For example, care must be taken to supervise children where traffic conditions change, child seats and seatbelts may not be readily available in cars and often need to be ordered in advance, and accommodation should be checked for safety.

High altitude

Acute mountain sickness can be difficult to recognise in young children, and they may not be able to describe their symptoms. It has been suggested in the past that young children should not sleep above certain altitudes. However, there are no data and no clear consensus.

Most mountain tourist sites are at or below 3000 metres. Many children travel to these locations without difficulty, but caution is advised, particularly if the location is remote, without rapid access to good medical care. Any child who becomes unwell at altitude should be assumed to have altitude illness unless a clear alternative diagnosis is obvious. The principles of management are the same as in adults.

See chapter 6.5, Altitude sickness.

Key readings

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7.3 Elderly travellers

The number of elderly people who are undertaking international travel – often to exotic destinations – is steadily increasing. It is estimated that approximately 15% of travellers are over the age of 65.

Although most aspects of pre-travel advice will not differ for older individuals, there are a number of points that need to be specifically considered.

Characteristics of elderly travellers

Coexisting medical illnesses

- Elderly people are more likely to have to coexisting medical illnesses that may put them at increased risk of health difficulties during travel. These include cardiovascular disease, respiratory disease, and diabetes.
- For those on medications, drug interactions with antimalarials and other prophylactic medications need to be considered, and advice regarding how to take medications when crossing into different time zones is important.
- Older people are more prone to falls and other injuries.

Age-related vulnerability to diseases

Reduced vulnerability

Prior exposure via natural infection is more likely in elderly persons for infections such as hepatitis A and measles. For example, more than 60% of people over the age of 50 in Australia have hepatitis A antibodies compared with <5% of 20-year-olds. This means that older individuals may already be protected, and serological testing for hepatitis A antibodies is recommended by the NHMRC for people born before 1950, prior to vaccination. For measles, individuals born before 1966 can be considered immune (unless serological evidence indicates otherwise).

Increased vulnerability

The elderly may be at increased risk of other travel-associated health problems. This is generally because of one of the following reasons:

- **Physiological changes**: Achlorhydria, which increases the risk of travel-associated diarrhoea due to agents such as cholera, typhoid and giardia, is more common in the elderly. Age-related decline in lung and cardiac function may make the elderly more prone to hypoxia when exposed to the low partial pressure of oxygen in aircraft cabins, and supplemental inflight oxygen may be required. Physiologic changes may also make older people more prone to other travel-associated conditions such as thromboembolism, heat stroke, jet lag and dehydration. Changes in the circadian rhythm and environmental stresses may promote psychological distress and confusion in the elderly.
- **Lack of routine primary immunisation**: For example, more than 80% of clinical tetanus in the developed world occurs in individuals >55 years of age, because they have missed out on tetanus vaccination.

Greater severity of travel-related illnesses

The elderly are more prone to severe infections and complications following infection with certain pathogens. For example, hepatitis A usually results in a relatively mild infection in the young, but the risk of severe infection increases with increasing age, and mortality rates are as high as 2% for patients >40 years of age. The mortality rate following typhoid infection is also higher in older individuals (approximately 3.3% in people over 50 years of age compared to 0.4% in younger people). Adults above 50 years also have increased risk of severe disease and death if they acquire yellow fever, Japanese encephalitis, pneumococcal infection or influenza. Thus immunisation against these infections should be particularly considered for older travellers. Malaria infection is also more severe in the elderly and thus anti-mosquito measures and prophylaxis are important; cardiac conduction defects are increased in this population and should be taken into account when considering mefloquine use.

Diminished response to vaccination

Delayed development of immune responses, decreased peak antibody responses, more rapid waning of protective antibodies, decreased protective efficacy, and increased side-effects have all been noted in elderly individuals after administration of certain vaccines. The relative importance of increased age in isolation from effects of other co-morbidities is debated, but the net observed effect is a decrease in the quantity and quality of immune responses in older individuals.

Increased side-effects from vaccination

The only vaccine that may cause increased side-effects in the elderly is the yellow fever vaccine. Although the practical implications of most of these findings are unclear, recent reports suggest that serious side-effects following yellow fever vaccine resulting in hospitalisation or death are more common in older individuals (0.2 per 100 000 doses overall compared to 1.8 per 100 000 doses if aged 65 years or more). This means that the risk of infection – as opposed to official entry requirements – needs to be considered when giving pre-travel advice, and a letter of vaccine waiver may be appropriate in some cases.

Pre-travel advice to elderly travellers

Pre-travel advice to older individuals may be more difficult because of co-morbidities, medications, physiologic changes and differing disease risks. However, there are no age limits for travel, and safe travel for the elderly is possible.

Some practical points include:

- individualise care
- early appointment for pre-travel advice (6–8 weeks prior to departure)
- perform a 'fitness to travel' assessment
- advise the older traveller to:

  - take out travel health insurance that covers trip cancellation due to illness and medical treatment overseas, including the costs of medical evacuation
  - carry a list of medications and a letter outlining the past medical history
  - ensure adequate supplies of medicines are carried or can be sourced during travel
  - carry medication in hand luggage
  - take medication as usual on the day of travel
  - inform the airline in advance if special assistance needed
  - consider prophylactic antibiotics to prevent travellers' diarrhoea
- consider an exercise program prior to travel.

Travel by the elderly is an important opportunity to update routine immunisations such as tetanus, pertussis, polio, influenza, and pneumococcal vaccines (see AIH for indications of pneumococcal vaccine).

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7.4 Expatriates and long-term travellers

A long-term traveller may be defined as someone travelling abroad for 6 months or more. Expatriates, on the other hand, include those who have taken up long-term residence in a foreign country, commonly for occupational purposes, and ultimately return to their country of origin. Expatriates may spend several months to several years in a foreign country, and may adopt many aspects of the host culture.

Health risks of expatriates

In addition to the health risks faced by short-term tourist and business travellers, expatriates and long-term travellers are at risk of many other health problems. The young and adventurous long-term travellers have an increased risk of acquiring infections such as gastrointestinal infections and malaria. Expatriates, comprising a diverse group of individuals – government employees, business people, aid workers and missionaries – have varying health risks. These not only include infectious diseases but also medical conditions such as

diabetes mellitus, asthma, ischaemic heart disease, and psychiatric and psychological problems.

Although travel and working in a foreign country is likely to be a rewarding experience for expatriates, relocation to a new country with different cultural practices and language barriers may result in considerable stress, anxiety, and social dislocation. In extreme cases, this may lead to drug and/or alcohol abuse. In a proportion of expatriates, the stress and anxiety associated with relocation and the inability to adjust to their new social and cultural environment results in an early return home. It has been found that 20–40% of all expatriates return home early because of their inability to adjust to the new culture.

Preparation for the expatriate traveller

Preparation for the expatriate traveller not only requires discussion of infectious disease risks but also the management of existing medical problems in a foreign country, managing the psychological stresses associated with living in a foreign country, and the problems that may be encountered with the assimilation of the host culture. Some may travel to work in relatively remote destinations and will

Box 1: Role of the sponsoring organisation

Individuals who travel to work as volunteers or missionaries should choose an organisation that offers good training, and medical, emotional and practical support. Often, talking to individuals who have worked with the organisation can provide the traveller with a tremendous insight into what lies ahead.

Careful consideration of the level of support provided by an organisation can help prevent avoidable problems, and make the time spent in a foreign country rewarding and enjoyable. Advise those working with an organisation to check on the following issues:

1. Financial arrangements of travel and relocation: Expatriates should establish before departure whether they and their families are required to cover the costs of travel and relocation. Some organisations completely cover these costs, but this is not always so, leaving some expatriates with the experience of a financial shortfall in a foreign country.
2. Medical support: Expatriates should know if the organisation provides medical support for them and their families, either directly or in the form of contact details of adequately trained medical practitioners in the host country. Ascertain if there is a carefully constructed plan for evacuation in the event of a medical emergency, and how this can be accessed by them should the need arise.
3. Language training: Language is a major barrier to social integration for expatriates. They should find out if the sponsoring organisation provides language training and whether paying the cost of such training is the responsibility of the traveller.
4. Social and educational support for spouse and children: Expatriates need to know whether cost of education, social supports and leave entitlements are part of the contract.

Box 2: What the travel-medicine practitioner should do for the expatriate

- Conduct a baseline health assessment.
- Conduct an abbreviated psychological assessment and refer on if necessary.
- Assess and explain health risks, both physical and psychological.
- Counsel on problems of adjustment and culture shock.
- Provide and advise on immunisation and malarial prevention.
- Counsel on other infectious health risks such as travellers' diarrhoea, STI, and rabies.
- Counsel on reduction of risk-taking behaviours.
- Check the role of the sponsoring organisation.
- Remind the need for dental check up.
- Provide or recommend reading material.

need to consider carefully whether or not their healthcare requirements will be provided for and met adequately. It is therefore important to provide long-term travellers and expatriates with thorough pre-travel screening and preparation.

The problem is largely solved if the expatriate is going to work for an organisation with an established program for its overseas employees. Psychological assessment has probably been performed. Nevertheless, go through the checklist above and discuss the issues in Box 1: Role of the sponsoring organisation.

For those without such support from an organisation, the travel-medicine practitioner will need to spend more time with the traveller and address the issues in Box 2: What the travel-medicine practitioner should do for the expatriate.

The pre-travel assessment

Expatriates should have a comprehensive pre-travel assessment, emphasising preventive health and medical issues common to all travellers. Start with a general baseline health assessment to identify underlying medical issues that may pose a problem after travel. Stress the need to know the level of medical support available at their destination and where adequate care can be found. Reinforce the need for the traveller to identify medical facilities soon after arriving at their destination, rather than waiting for a medical emergency to arise. Many expatriates and missionaries will have these issues dealt with by the organisation that has arranged their travel. However, this may not be the case for long-term travellers. Finally, provide appropriate immunisation and malaria prophylaxis.

Baseline health assessment

The pre-travel medical consultation for the expatriates needs to be more comprehensive than for the short-term traveller. Their needs must be individualised,

depending on the destination and duration of travel and the activities the travellers are likely to engage in while away.

The consultation begins with a comprehensive history of the individual's medical and mental health and a thorough physical examination. For those with underlying chronic medical problems, such as diabetes mellitus, cardiac failure and asthma, laboratory tests may need to be done to determine if they are medically fit to travel.

Travellers with chronic medical conditions should have a thorough understanding of their illness and its management. They should be reviewed by their family doctor or specialist before travel, and have a letter containing details of their illness and medications prescribed. Discuss with them how their illness can be best managed in the new country. For example, a traveller who suffers from asthma must have a clear understanding of how to monitor the severity of their disease, and a practical asthma management plan. A diabetic traveller on insulin will need to consider how best to correctly store their insulin, monitor blood sugars, and how to manage hypoglycaemic and hyperglycaemic episodes. Travellers with ischaemic heart disease must ensure that they have adequate supplies of anti-anginal medications and also have an appreciation of symptoms that may suggest progression of their coronary artery disease, thus prompting a medical assessment and avoidance of a myocardial infarction.

Psychosocial assessment

The pre-travel assessment must also include how the traveller may be affected by living and working in a foreign country and culture. It should also evaluate the potential impact of relocation on the traveller's family, particularly on children. Psychological assessment is usually part of the selection procedure of organisations sending expatriates abroad, and the travel-medicine practitioner is usually not involved. Expatriates without organisational support may come to the travel-medicine practitioner for their entire pre-travel assessment and care. A brief psychological interview is indicated for such patients. If anything untoward is found, the intending expatriate should meet with someone with greater expertise in this area. Addressing these factors will help to avoid more serious problems once the traveller is in a foreign country. The following information should be sought at the interview:

- present and previous psychiatric or psychological problems (for example, depression, obsessive–compulsive tendencies, eating problems, panic attacks, alcohol or drug misuse)
- existing stress issues and how they are handled (for example, recent bereavements, illness in family, ageing parents)
- treatment for psychiatric or psychological disorders: anti-depressant or other psychiatric medication, counselling

- family history of psychiatric illness.

Culture shock

For inexperienced expatriates, raise the subject of culture shock. Some degree of culture shock is normal when one moves to an entirely new set of living conditions. Culture shock is more than adjustment to a new country, new working environment, different language customs and community life. It can cause real psychological problems, such as insomnia, irritability, profound homesickness, depression, drug and alcohol misuse, and a general inability to cope. The basic cause of culture shock is the abrupt loss of the familiar, which in turn causes a sense of isolation and diminished self-importance. It is important for organisations and families to be aware of and address these potential issues of loneliness and alienation both before and during the overseas assignment.

Box 3 contains some measures to ameliorate culture shock. The website <http://international.engr.wisc.edu/preparing/cultureshock.php> has a document entitled 'How to cope with culture shock' by an American student service.

Immunisations

Immunisations that are required by expatriates and long-term travellers are discussed in detail elsewhere in this manual. However, a number of infections are particularly relevant for the expatriate.

Box 3: Measures to prevent culture shock from being overwhelming

- Recognise that a feeling of alienation is normal and that culture shock exists.
- Be aware that it will probably affect you one way or another, but that it doesn't last forever.
- Anticipate it.
- Be well prepared and go with good information ahead of time.
- Consult others who have been on similar overseas assignments.
- Keep in mind that it is acceptable to seek help.
- Take care of physical health.
- Mix socially with the local people.
- Learn the local language.
- Do not withdraw from the community.
- Don't expect to achieve all that you have planned quickly.
- Be satisfied with small gains and victories.
- Don't abuse alcohol, and avoid drugs of addiction.
- Keep in touch with home.
- Be positive and accept the idea that while it may be somewhat painful, culture shock can be a very valuable experience.

Hepatitis A

Hepatitis A is among the most common vaccine-preventable diseases in travellers to Asia, Africa, South America and the Middle East. The risk of acquiring hepatitis A in non-immunised travellers varies between 6 and 28 cases per 100 000 months of stay in developing countries. The risk is higher in long-term travellers and expatriates in whom up to 48% of those residing in Africa for 18–35 months will seroconvert to hepatitis A virus. Vaccination with hepatitis A vaccine is recommended for all long-term travellers and expatriates to high-risk endemic countries.

Hepatitis B

Hepatitis B infection remains a major health problem, particularly in developing countries in Asia, Africa, the Middle East and the Pacific Islands. The chronic carrier rates in these regions of the world range from 10 to 20%.

In travellers the risk of acquiring hepatitis B infection is substantial, with an overall risk of 1 per 2500 travellers in highly endemic countries. In expatriates the risk of developing symptomatic hepatitis B infection is as high as 60 cases per 100 000 persons per month of stay, and 80–420 cases per 100 000 persons per month of stay for asymptomatic infection. The risk of developing hepatitis B infection increases over time, with 10.5% developing seroconversion after 18–35 months in Central and West Africa. It has been reported that up to 11% of missionaries in Sub-Saharan Africa will develop seroconversion during each of the first 2 years, with a median attack rate of 4.2% per year thereafter. Consequently, it is important to ensure that long-term travellers and expatriates are fully vaccinated against hepatitis B.

Typhoid fever

Typhoid fever is common throughout Asia, Africa, the Middle East and South America, and immunisation against this infection is recommended for travellers visiting these areas.

In developing countries the incidence of typhoid fever is greater than 100 cases per 100 000. The risk in travellers depends on the travel destination and duration of travel. The incidence of typhoid fever in travellers to Chile, Indonesia and the Indian subcontinent is as high as 100 cases per 100 000, compared with 4.38 cases per 100 000 in the remainder of South-East Asia, 1.27 cases per 100 000 travellers to South America, and 0.8 cases per 100 000 travellers to the Caribbean. Vaccination for typhoid fever is recommended for all long-term travellers and expatriates to endemic areas.

Meningococcal vaccination

Expatriates and long-term travellers have longer durations of travel and often have increased contact with the local population, putting them at higher risk of

acquiring meningococcal disease than the short-term traveller. Therefore in those traveling to endemic areas meningococcal vaccination is indicated (see chapter 2.9).

Japanese encephalitis (JE)

The risk of travellers acquiring JE depends on several factors, including travel during the peak transmission season, the location and duration of travel, and exposure in rural areas. For example, the JE attack rates in US military personnel stationed in Asia ranged from 0.05 to 2.1 (median 0.9) per 10 000 per week. Vaccination for JE should be considered for expatriates and long-term travellers living in endemic countries.

Rabies

Rabies is an important disease about which to counsel expatriates and long-term travellers. For expatriates living in rabies-endemic regions, the risk of exposure is approximately 1 per 1000 volunteers per month. Children are at particular risk. The risk of a child being bitten by a dog is estimated to be four times greater than that of an adult. In addition, children are more likely to be bitten on the face, neck and hands, and this is associated with a greater likelihood of developing rabies than bites to limbs or trunk. Pre-exposure vaccination is therefore recommended especially for:

- families with children and pets
- expatriates and travellers with limited access to medical care and transportation or who travel into remote regions
- expatriates and travellers who will be working with animals.

Children should be educated never to approach dogs or unfamiliar animals, and to stay away from any animal displaying unusual behaviour. It is also important to educate children to report bites immediately to an adult in order to commence post-exposure treatment promptly.

Tuberculosis – BCG

The risk of latent mycobacterium tuberculosis is about 3% per year for aid workers and missionaries working in refugee camps. Children attending schools are also at an increased risk of developing TB.

Children under the age of 5 years should receive BCG before travel to reduce the risk of developing disseminated disease and TB meningitis. We recommend BCG for tuberculin-negative individuals under the age of 35 years who will be living for long periods (>6 months) in high-risk countries (defined as having an incidence >100 per 100 000 population), in particular healthcare workers in countries with multidrug-resistant *M tuberculosis*. See chapter 2.16, Tuberculosis, for an

alternative strategy involving the performance of a Mantoux test before departure and after return in order to determine if infection has occurred while abroad.

Malaria prevention

Malaria is the leading cause of death among expatriates who die from infectious diseases. The incidence of malaria in expatriates ranges from 31 per 1000 per year in Asia to 209 per 1000 per year in West Africa. The approach to prevention of malaria, including the various options for expatriates, is comprehensively covered in Chapter 3. Reinforce the following points to expatriates and long-term travellers:

- Anti-mosquito measures work: use of repellents, bed nets, and permethrin impregnated clothes can reduce the risk of contracting malaria by ten-fold.
- Compliance with chemoprophylaxis is difficult for expatriates to maintain.
- Emphasise that there are no chemoprophylactic drugs that are completely effective, and any fever can be due to malaria.
- Stress that the risk of severe disease is higher in children and pregnant women.
- If emergency self-treatment is prescribed, go through the 'when and how' carefully with the traveller (see chapter 3.4).
- If the use of a self-diagnosis kit is considered, train the expatriate in its correct use, and warn that errors can occur when the test is performed by ill persons.

Diarrhoeal diseases

Diarrhoeal diseases related to bacterial and parasitic infections are common among expatriates and long-term travellers. The incidence of giardiasis in long-term travellers is 660 cases per 100 000 travellers per month of stay in developing countries.

Long-term compliance with preventive measures, as stated in Chapter 4, Travellers' diarrhoea, is close to impossible for expatriates and long-term travellers. Adherence to basic hygiene principles and drinking boiled or bottled water can reduce the number of attacks. Teach them how to self-treat acute and prolonged forms of diarrhoea.

Sexually transmitted infections

Up to 40% of male and 30% of female expatriates report a casual sexual encounter, and many of these are unprotected. Hence, sexually transmitted infections are a health risk for expatriates. Reinforce safe sexual practices and emphasise the risk of acquiring HIV as a consequence of unprotected sexual encounters.

Other infectious diseases

Long-term travellers and expatriates may acquire infections that are seen infrequently in short-term travellers. Many of these infections are covered in Chapter 5, Non-vaccine-preventable infections. Appendix 1, Common travel destinations, and the tables in Chapter 5 list the important infectious hazards common in various destinations and associated with different activities. While most of these infections are uncommon, the risks can be reduced by understanding the mode of spread and how best to avoid them.

Many parasitic infections, including helminths, are not a frequent problem for short-term travellers, but may be a more significant problem for expatriates and long-term travellers. The incidence of helminthic infections is estimated at 97 cases per 100 000 travellers per month of stay in developing countries. Helminthic infections include strongyloidiasis, hookworm, filariasis, schistosomiasis, cysticercosis and hydatid disease. Other infections, such as African and American trypanosomiasis, leishmaniasis, onchocerciasis and endemic fungal infections are rarely seen in short-term travellers, but may occur in long-term travellers and expatriates.

Other health risks

Risks to health from violence, motor-vehicle accidents, swimming, misuse of drugs and alcohol are greater among expatriates than among short-term travellers. Safe behaviour can prevent more travel-related illness and deaths than specific vaccines and prophylactic drugs (see Chapter 1).

Conclusion

The counselling of expatriates, their families and long-term travellers is complex and time consuming. They may need to return for several consultations in order to cover the many issues discussed above. Proper planning, advice and immunisations can help to avoid many problems after departure.

Finally, provide expatriates and long-term travellers with a medical consultation after their return in order to attend to medical, psychological and infectious disease issues that may have arisen as a consequence of their travels. This should be considered an essential component of providing these travellers with complete health advice and care.

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O'Brien DP, Biggs BA. Malaria in the expatriate and long-term traveller. Australian Prescriber 2002; 25(3):66–9.

Toovey S, Moerman F, Van Gompel A. Special infectious diseases risks of expatriates and long-term travelers in tropical countries. Part II: infections other than malaria. J Trav Med 2007; 14(1):50–60.

7.5 Visiting friends and relatives

People travelling overseas to their country of origin to visit friends and relatives (VFR travellers) include previous immigrants and refugees returning to their country of birth, international students travelling home in semester breaks, and migrant workers. As a group they are at a higher risk of acquiring many travel-related infections, including malaria, typhoid, tuberculosis and HIV. This is due to a number of factors including:

- they are often travelling back to a more resource-limited setting
- they usually stay in close proximity to the locals, often in rural areas, thus experiencing similar conditions and sharing similar eating and drinking patterns
- they are often unaware of their travel risks, so are less likely to seek pre-travel advice, or to take prophylactic medication, even though previous immunity has often waned
- their travel is often of a longer duration.

Pre-travel advice

For reasons stated above, VFR travellers need to be specifically targeted prior to travel, with attention paid to education, vaccination and appropriate chemoprophylaxis. As they are less likely to access pre-travel health care, family doctors will need to be pro-active, and discuss these issues with their patients on learning that they intend to visit friends and relatives in their country of origin.

Malaria

VFRs travelling to an endemic malarial region are often under the impression that they have immunity to malaria from prior residence there. However, any partial immunity they may have had is lost within about 6 months of leaving the area, and thus on return they are again at risk of clinical malaria. Furthermore, they often reside in rural areas, stay longer, and are less likely to pay attention to mosquito avoidance measures than other travellers, thus resulting in higher rates of mosquito exposure. In addition, VFRs are much less likely to take anti-malarial chemoprophylaxis. These factors combine to make the rates of malaria significantly higher for VFRs than for other travellers. (For options see Chapter 3, Malaria prevention.)

Hepatitis A

VFR travellers have a higher rate of hepatitis A acquisition than other travellers, mainly in the younger age group. The adults may have been born in a

resource-limited setting and thus acquired infection and then immunity at a young age, but their children have often been born in a more developed setting and have not been previously exposed. They are therefore at risk of hepatitis A acquisition – a risk their parents may not be aware of.

Other infections

VFR travellers present more often with serious, potentially preventable travel-related illnesses than other travellers. In particular, following travel, they are at an increased risk of presenting with typhoid fever and STIs acquired during their travel to high endemicity countries. For reasons mentioned previously, including the travellers' lifestyle, behaviour, and culture, this risk undoubtedly applies to many other travel-related infections, although current data are lacking.

Key readings

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7.6 Travellers with cardiovascular problems

Cardiovascular disease is the leading cause of death worldwide, and among international travellers. Most persons with stable heart disease can travel safely. For those with an unstable condition the doctor and patient must decide whether the trip is worth the risk. It is definitely not advisable for any person with advancing or unstable heart disease to plan a major international trip, especially if the destination is at high altitude or in a remote location where medical assistance will not be readily available.

Individuals with cardiac problems, including coronary artery bypass surgery, who are asymptomatic while performing everyday activities at sea level, generally have no problems at altitudes up to 2400 metres (8000 feet). This is equivalent to the level of oxygen in pressurised aircraft cabins. People able to walk a city block or climb a flight of stairs without shortness of breath can generally compensate for reduced oxygen in the aircraft cabin air.

All patients with medication needs should carry in their hand luggage ample quantities of routine and emergency drugs they may require. A detailed letter

from the treating doctor/s should be carried, including emergency contact details, recent test results, and a copy of the most recent ECG. The high sodium content of many airline meals may be problematic for some travellers, and special dietary requirements should be notified to airlines before departure. It is also advisable to avoid alcohol and caffeine.

Patients with coronary artery disease

Travel following successful coronary bypass surgery is generally not a problem. Exercise testing is also generally not required unless clinically indicated. If persistent cardiac ischaemia is suspected, a cardiac stress test is a useful investigation to predict the likelihood of recurrent myocardial ischaemia. An abnormal scan would weigh strongly against a traveller going to a medically underserviced destination.

Severe angina or heart failure

Patients with severe angina or heart failure (unable to walk 50 m or climb 15 stairs without symptoms) need supplemental inflight oxygen. This can be intermittent or continuous, but usually only 2 or 4 L/min are possible. The airline must be advised in advance and the patient should be aware that extra cost might be incurred. Patients should also be educated that alcohol worsens the effects of hypoxia.

Pacemakers

Air travel is safe for passengers with pacemakers; however unipolar-lead pacing systems may be susceptible to electronic interference during flight. In addition, airport security screening devices, especially hand-held ones, may interfere with both unipolar-lead pacing systems and implanted automatic defibrillators, thus advice should be sought prior to undergoing these checks. If necessary a letter from a doctor or pacemaker company should be carried that allows exemption

Cardiovascular contraindications to air travel

- Recent acute myocardial infarction – no travel for 3–4 weeks after event
- Uncontrolled arrhythmias
- Uncontrolled hypertension
- Angina during normal living activities
- Recent angioplasty – no travel for 3 days
- Uncontrolled congestive heart failure – may travel 2 weeks after CHF is controlled
- Pulmonary hypertension, with or without cor pulmonale
- Severe symptomatic valvular heart disease
- Recent cardiac surgery – no travel for 2 weeks after surgery.

from electronic checks in favour of a hand search. Travellers should know what type of pacemaker they have and how to arrange to have its function checked. Long-distance telephone connections from foreign countries may be of poor quality and interfere with telephone regulation of pacemakers.

Flight attendants on commercial aircraft are trained in basic first aid. An increased number of airlines have automated external defibrillators on board their planes and train flight attendants and senior staff in semi-automatic defibrillation.

Key readings

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7.7 Travellers with chronic lung disease

Air travel

Airline travel exposes passengers to conditions of relative hypoxia with cabin pressures equivalent to an altitude of 5000–8000 feet above sea level. A pressurised aircraft flying at 19 688 metres has a cabin altitude equivalent to 1676 metres. The average person ascending from sea level to 1676 metres would experience a decrease in the PO_2 of the surrounding air from 159 mmHg to 128 mmHg, and a decrease in PaO_2 from 107 mmHg to 74 mmHg.

Healthy passengers can easily tolerate this degree of hypoxia, but it may cause difficulties for patients with reduced pulmonary capacity. In addition, the reduced cabin humidity levels (19%) may thicken pulmonary secretions, causing problems for those with conditions such as chronic bronchitis and tracheostomies.

Fitness to fly

The situations when travellers with respiratory problems should not fly are set out in chapter 6.1, Fitness to fly. Other patients with respiratory symptoms may need further assessment. Patients with poor exercise tolerance (for instance, those unable to walk 50 m or climb 15 stairs without significant symptoms) should be reviewed by a respiratory physician; they may well require supplementary oxygen during air travel.

Patients breathing air at sea level with a haemoglobin oxygen saturation above 95% will not need oxygen in flight, whereas it will be required for those with a

saturation below 92% or a PaO_2 <70 mmHg. Dyspnoea at rest is generally a contraindication to flying.

Consideration should be given to performing pulmonary function tests, arterial blood gas measurements, and sometimes formal assessment in a hypobaric chamber.

Concerns about fitness to fly can usefully be discussed with the medical officer of the airline involved; all arrangements should be made well in advance of travel. Most airlines use a standard Passenger Medical Information form to communicate arrangements required for passengers with medical needs. This information is confidential, but may be transmitted between airlines. It includes questions about diagnosis, prognosis, desired oxygen requirements, feeding, and toileting.

Before travel

Travellers should discuss their travel plans with their physician well before travelling. They should understand their condition, its monitoring and control, and have a clear emergency plan.

- They should carry a letter from their doctor/s describing their condition/s and medications, and their most recent test results.
- Medication supplies should be more than sufficient for the duration of the trip. A supply should be kept in the carry-on luggage.
- Patients with asthma should have a clear asthma management plan, and travel with a peak flow meter and an adequate emergency supply of inhaled bronchodilators and corticosteroids.
- Optimise lung function prior to travel with such things as bronchodilators and corticosteroids.
- Patients with hypoxaemic, hypercapnic chronic lung disease may benefit from the addition of acetazolamide 250 mg twice daily. This stimulates breathing and is useful prior to and during flight. It is discontinued after arrival at destination. The use of acetazolamide is associated with the development of hypokalaemia, which may worsen respiratory function; consequently it should not be used for a prolonged period of more than 3 days. However, we recommend before prescribing acetazolamide that an opinion should be sought from a respiratory physician for individuals with severe COPD wanting to undertake air travel.
- All travellers with chronic lung disease should receive influenza and pneumococcal vaccines.
- They must stop smoking for at least 48 hours before flight.
- Consideration should be given to carrying a course of antibiotics (e.g. doxycyline or augmentin) for presumptive self-treatment of chest infections, if medical help is not easily available.

- High altitude destinations should be avoided due to the relative hypoxia (above 2000 m).
- Travellers should be given names of doctors or medical centres (if necessary, English-speaking) in foreign countries, and have check ups as recommended by their doctor/s at home. Particularly for long-term travellers and expatriates, familiarity with available local medical facilities and personnel before the need for their services arises can reduce delay, anxiety and confusion when care is needed.
- Adequate travel health insurance should be arranged.
- A travelling companion to render assistance is particularly valuable for those with more severe or unstable conditions.

In-flight oxygen

This can be provided by some but not all airlines, and most international airlines will not permit passengers to supply their own oxygen cylinder. On Australian domestic flights passengers can carry their own oxygen cylinder.

If oxygen is required for a passenger, the airline must be advised and details must be specified: intermittent or continuous, desired flow rate (usually only 2 or 4 L/min is possible) and means of delivery (face mask, nebuliser or nasal prongs). There may be a fee. Most airlines will also require a doctor's clearance letter at least 48 hours prior to the flight. On some airlines, large oxygen requirements can be catered for by a large (3800 L) cylinder strapped into a row of seats (which must be paid for).

Nebulisers for use in flight can either be electrically operated (approved by the airline and arranged in advance), battery-operated, foot-operated, or oxygen-driven (these also require prior arrangements with the airline).

During air travel

Patients with COPD should avoid overeating (abdominal distension), alcohol, smoking and sedatives.

Their travelling companions should be aware that headache, fatigue, sleepiness, dizziness, impaired memory or judgement, incoordination, personality changes and visual impairment may be signs of hypoxia, and that medical assistance is required.

Key readings

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7.8 Travellers with diabetes

Travelling exposes people to unusual food, changes in time zones, a variety of diseases, and varying amounts of exercise.

Intending travellers with diabetes should discuss their travel plans with their general practitioner and diabetes specialist. It is advisable that diabetic travellers seek pre-travel advice at least 4–6 weeks before departure in order to optimise their control and review management plans of intercurrent illness, particularly involving diarrhoea, vomiting and fever. They should be reminded of their increased susceptibility to a range of infections and, in many cases, to more severe and complicated disease.

General advice

Advise the diabetic traveller to carry a medical kit containing the following:

- a letter from the doctor outlining their condition, control, insulin regimen, medication, acute and chronic complications, and contact details
- a diabetic alert card, identification tag or bracelet
- sufficient insulin to last the entire trip (at least for trips lasting up to several months)
- U-100 syringes to last the entire trip
- at least one bottle of regular (short-acting) insulin
- blood glucose testing equipment
- ketone test strips (for use during illness)
- quick-acting carbohydrate (e.g. sweets, jellybeans or packaged juice)
- slow-acting carbohydrate (e.g. dried fruits, crackers, sandwiches or nuts)
- glucagon ampoule (1 mg with 1 mL diluent), although the traveller must be well informed of its use.

It is important to be well equipped, as supplies may be difficult to find in other countries. Insulin will remain stable for months at room temperature (20–24°C), but should be protected from extreme heat and freezing cold.

Travellers should take twice as much insulin, syringes and medications as required and divide them between their hand luggage and that of their travelling companion. Alternatively, half should be kept in check-on luggage.

Travellers who require insulin should obtain an accurate itinerary of their journey with departure and arrival times, duration of flight sections, stopovers and approximate meal/snack times, as adjustment to insulin dosage during the flight may be necessary. The traveller should also inform the airline in advance to arrange a suitable diet.

Concern about possible problems with customs or immigration authorities due to needles and syringes or other items of medical equipment can be allayed by a doctor's letter stating their medical need. A second signed copy translated into the appropriate language could also be carried. We have not heard of patients with diabetes having any problems in travelling with their equipment and insulin.

A list of medications is useful in case replacements are needed. Carry written translation of a few essential phrases (for instance, 'I have diabetes' and 'I have diabetes. Could you please quickly give me some sugar or something to eat').

Ensure travelling companions know the early signs of hypoglycaemia, and what to do if they suspect it.

Pneumococcal and influenza vaccines should be updated. Travellers should also be advised to maintain adequate hydration and to consider antibiotic prophylaxis for the prevention of travellers' diarrhoea during short trips.

If travel involves a lot of walking or trekking, it is important to avoid new shoes that may cause blisters, and each night the feet should be checked for signs of injury.

Insulin dosage

Insulin dosage should not be of concern during travel unless there has been or will be a marked change in exercise or diet. Any rapid change in time zone will also have an effect. It is important to emphasise that tight diabetic control may run the risk of hypoglycaemic episodes while crossing multiple time zones. Consequently, it may be safer to accept higher than normal glucose readings during travel. It is essential that the traveller monitor blood glucose frequently (every 4–6 hours), particularly while en route and crossing multiple time zones.

Airflights in a northerly or southerly direction do not result in significant time changes and should not interfere with insulin dosage. Flights in an easterly or westerly direction may result in substantial changes, which must be considered when adjusting insulin dosage. This is not important if the travel time between the Australian departure point and the destination is <4 hours.

Most diabetics who are familiar with managing their conditions simply use premeal glucometer readings and short-acting insulin when eating meals with or without long-acting insulin before sleep on the plane. This method copes with unforeseen flight delays and schedule changes, is applicable to all flights, and is simple to remember. The usual regimen should be implemented on the morning after arrival in the destination.

Some seasoned diabetic travellers wear two watches or watches with dual time pieces, one with Australian time and the other with actual/local time, and take insulin as per Australian time, adjusting to local time on arrival at destination.

The following schedules have been recommended for **travellers crossing time zones**:

Table 7.8.1 Insulin adjustment

Travelling east across multiple time zones (day is shortened)

	Day of departure	First morning at destination	10 hours after morning dose	Second day at destination
Single-dose schedule	Usual dose	2/3 usual dose	Remaining 1/3 of morning dose if blood sugar over 13 mmol/L	Usual dose
Two-dose schedule	Usual morning and evening doses	2/3 usual morning dose	Usual evening dose + remaining 1/3 of morning dose if blood sugar over 13 mmol/L	Usual 2 doses

Note: For westward travel on the return journey people should use the **westbound** schedule.

Travelling west across multiple time zones (day is lengthened)

	Day of departure	18 hours after morning dose	First morning at destination
Single-dose schedule	Usual dose	1/3 of usual dose followed by meal or snack if blood sugar over 13 mmol/L	Usual dose
Two-dose schedule	Usual morning and evening doses	1/3 of usual dose followed by meal or snack if blood sugar over 13 mmol/L	Usual 2 doses

Note: For eastward travel on the return journey people should use the **eastbound** schedule.

- **Travel across few time zones** – For a time change of 5 hours or less, frequent testing of blood glucose and taking insulin according to the usual schedule (using local time) will usually suffice. Supplemental regular insulin (with snacks or meals) may be used if needed.
- **Travelling east across six or more time zones** – The usual insulin dose should be taken on the morning of departure. If an evening dose is taken, it should be given at the usual time. On the first morning after arrival, only two-thirds of the usual insulin dose should be taken. If the blood sugar exceeds 13 mmol/L (240 mg/dL), the remaining one-third of the morning dose should be added to the evening regimen. On the following morning, and for the remainder of the trip, the usual insulin dose should be resumed using local time.
- **Travelling west across six or more time zones** – The usual insulin dose should be taken on the morning of departure. For persons who normally take an evening dose, the 'evening' dose should be given 10–12 hours after the morning dose. Eighteen hours after the morning dose, for persons who

usually take a single injection or two doses of insulin daily, a dose equal to one-third of the morning dose should be taken if the blood sugar is above 13 mmol/L. A snack or meal should be taken with the insulin doses. On the following morning, and for the remainder of the trip, the usual insulin dose(s) should be resumed using local time.

Key readings

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7.9 The HIV-infected traveller

Travel is increasingly common among HIV-infected persons, with a previous study reporting 45% travelling within their own country and 20% travelling abroad over a 2-year period. This has been significantly contributed to by the advent of antiretroviral therapy (ART) and the restoration of relative immune competency in most of those who take it. However, such travel, especially to developing countries, poses a number of additional HIV-specific issues and risks, and these need to be carefully addressed by a health practitioner experienced in both HIV and travel medicine. Despite this, it has been shown that almost half of HIV-infected travellers do not consult a physician prior to travel, fewer (12%) receive health information specifically related to their HIV infection, and only one in 18 who travel internationally consult a travel-medicine expert.

Map 19 shows the estimated prevalence of HIV in people aged 15–49 years worldwide.

General considerations

- Many infections encountered by travellers, including many vaccine-preventable diseases such as typhoid, hepatitis B and influenza, are more frequent and associated with **increased morbidity and mortality** in HIV-infected persons.
- Clinical findings associated with infection may be atypical, delaying correct diagnosis and treatment. Several infections may be present simultaneously.
- The protective efficacy of vaccines may be reduced, and there is an increased risk of **adverse effects from immunisation** with live vaccines. This is usually in proportion to the degree of immunosuppression.
- Persons with HIV infection are more likely to have **adverse reactions to drugs** used to treat and prevent infection (e.g. ampicillin, amoxycillin–clavulanic acid, ciprofloxacin and co-trimoxazole).
- Complications of HIV and its treatment, unrelated to travel, may develop at any time. Access to good medical care experienced in HIV management may be difficult.

Today most international travel is feasible. However, for those with advanced HIV disease and severe immunosuppression, travel for a prolonged period or to developing countries may not be medically recommended.

International travel restrictions

A number of countries restrict the entry of foreigners with HIV infection or AIDS, and insist on HIV-antibody testing for foreigners as a requirement for entry. These regulations apply mostly to immigrants, students, workers, and others applying for long-term entry permits, although in a few countries tourists staying for periods as short as 2 weeks are required to be tested. Some countries insist on HIV testing after arrival and will not accept results of tests conducted elsewhere.

For details of current restrictions, travellers should (anonymously) contact the consulates or embassies of countries to be visited. Updated information on HIV-related travel and residence restrictions for various countries is also available on the internet at <www.hivtravel.org>.

Immunisations

The benefits and risks of immunisation for international travel need to be carefully considered for persons infected with HIV. It has been shown that antibody response to many vaccines reduces as the CD4 lymphocyte count declines, however ART often reduces this effect. Therefore, vaccines are optimally given early in the course of HIV disease, prior to the development of significant immunosuppression, or, if late, preferably after commencement of ART once immunological function has improved (i.e. CD4 count >200 cells/mm^3) and viral suppression achieved (undetectable viral load for at least 6 months). The most immunogenic regimen should be used (e.g. double usual dose hepatitis B vaccine, intramuscular rather than intradermal administration of rabies vaccine), and it may be useful to measure post-immunisation antibody responses.

Concerns have been raised whether vaccine-induced immune stimulation affects HIV disease progression. Transient increases in HIV replication, reflected by rises in plasma HIV viral titres, have been observed to follow vaccination for influenza, tetanus, pneumococcus, hepatitis B, cholera and rabies. There is concern that this may lead to accelerated HIV disease progression, though presently available clinical data show no evidence to support this. In addition, these rises are transient, and similar and often more sustained rises in plasma HIV titres occur when HIV-infected persons develop the diseases the vaccines are designed to prevent, and these diseases can cause considerable damage. Therefore we believe that the benefits of immunisation outweigh the above theoretical risks, if there are strong indications for their use.

In general, HIV-infected persons should not receive live vaccines. However, because of the increased severity and occasional lethality of measles in HIV-infected persons, and the high mortality of yellow fever, exceptions for these two infections are made (see below). In addition it has been shown that it is safe

Table 7.9.1 Immunisation schedule for persons with HIV

Routine immunisation	Recommended for HIV-infected persons	Immunisation for HIV-infected travellers
Tetanus/diphtheria/pertussis Poliomyelitis Measles Hepatitis B H. influenzae (<5 years)	Pneumococcal Influenza	Yellow fever Hepatitis A Typhoid Meningococcal Japanese encephalitis Rabies Plague Cholera
Safe vaccines	**Unsafe vaccines**	**To be considered individually**
ADT or DTP	BCG	Measles
Cholera – injectable or oral inactivated (Dukoral)	Sabin vaccine (OPV)	MMR
Haemophilus influenzae type b conjugate vaccine	Typhoid – oral	Yellow fever (only if CD4 count >200 $\times$ 10^9/L)
Hepatitis A	Cholera – oral live attenuated (CVD 103 HgR)	Varicella-zoster (children)
Hepatitis B	Varicella-zoster (adults)	
Influenza	Intranasal live influenza	
Japanese encephalitis		
Meningococcal		
Plague		
Pneumococcal		
Rabies		
Salk vaccine (eIPV)		
Typhoid – inactivated		

to vaccinate for varicella-zoster virus in children with CD4 cell percentage greater than 25%.

Routine immunisations

- **Diphtheria and tetanus toxoid (ADT)**: If a primary course has previously been received, a booster dose should be given if one has not been administered within the last 10 years.
- **Polio**: Live oral polio vaccine (Sabin) is contraindicated in HIV-infected persons. The inactivated polio vaccine (IPV) should be used for primary or

booster immunisation against polio. Vaccine efficacy appears to correlate inversely with progressive stages of HIV infection.

- **Measles–mumps–rubella (MMR)**: In HIV-infected persons, measles may be a devastating disease, with a mortality of up to 40%. Persons may be considered to be immune if they have a history of physician-diagnosed measles or protective levels of measles antibody. In addition, persons born in Australia before 1966 are likely to be naturally immune. Testing for measles antibody is useful to identify those who are susceptible.

  Previously the risk of severe measles had been thought to outweigh the theoretical risk of the live vaccine in HIV-infected persons. However, a fatal case of MMR-associated measles pneumonitis in a 21-year-old man with AIDS has led to more conservative recommendations. The NHMRC, the CDC and the American Academy of Pediatrics currently recommend the use of MMR for children with HIV infection at 12 months of age, except for those who are severely immunocompromised (CD4 lymphocyte count $<750 \times 10^9$/L for children aged <12 months; $<500 \times 10^9$/L for children aged 1–5 years; or $<200 \times 10^9$/L for those aged ≥6 years, or CD4 lymphocytes <15% of total). For susceptible adults it is usually not recommended if the CD4 count is less than 200×10^9/L.

  Due to the high rates of measles in many developing countries, we still recommend MMR vaccine to susceptible HIV-infected long-term travellers and expatriates with CD4 lymphocyte counts less than 200×10^9/L who are able to make an informed choice.

  Response rates to the vaccine among HIV-infected persons are reduced, ranging from 18 to 58% in those with symptoms, and from 60 to 100% in those without, with improved response rates in those taking ART. HIV-infected patients also experience early loss of protective antibody. However, **immunoglobulin** may provide a useful alternative means of protecting severely immunocompromised travellers against measles.

- **Hepatitis B vaccine**: HIV-infected persons have a high risk of hepatitis B exposure due to shared modes of transmission, and once infected, an increased risk of chronic carriage and complications of infection. Therefore, unless already immune, the HIV-infected traveller should be vaccinated. The vaccine is safe, but the immune response may be poor. Vaccination should ideally occur before significant immunosuppression has developed (CD4 <500) or after ART has restored the CD4 count to greater than 350 cells/mm^3. Twice the normal dose should be administered (i.e. double the normal volume of vaccine or a standard dose of the increased strength dialysis formulation of vaccine) on four (rather than three) occasions at 0, 4, 8 and 24 weeks. If it is given, the serologic response should be checked 4–8 weeks post-vaccination. Pre-vaccination screening for hepatitis B is often worthwhile as many will have previously been infected. The combined hepatitis A and B vaccine is not suitable, as it contains only the standard dose of hepatitis B surface antigen.

- ***Haemophilus influenzae* type b conjugate vaccine** should be considered for children <5 years.
- **Influenza**: The NHMRC recommends annual inactivated influenza vaccine for **all** HIV-infected persons as they are at increased risk for complications of influenza. Antibody response rates to the vaccine are reduced, but it appears the vaccine still offers good protection even in those with CD4 lymphocyte counts below 200×10^9/L. Live intranasal influenza vaccination (not currently available in Australia) is contraindicated in HIV-infected people.
- **Pneumococcal**: Invasive pneumococcal infections are more common and severe in HIV-infected persons. Studies of the 23-valent polysaccharide vaccine have shown reduced antibody responses in proportion to the level of immunosuppression, but have still demonstrated protective efficacy. However, there is no demonstrable benefit to re-immunisation after 5 years. Clinical efficacy data supports the use of the newer 13-valent conjugate vaccines in children.

  All HIV-infected persons should receive pneumococcal vaccination regardless of travel. The NHMRC recommends that children <10 years should receive the newer 13-valent conjugate vaccines, whereas older children and adults should receive the older 23-valent polysaccharide vaccine.
- **Varicella-zoster**: Acute varicella is likely to be more severe in HIV-infected individuals, with high rates of disseminated disease, although data to support this are lacking. In addition rates of zoster are increased. However, the potential for dissemination of the live attenuated vaccine means it is contraindicated in adults. Nevertheless, it has been shown that in HIV-infected children with CD4 cell percentages greater than 25% the vaccine is safe. Thus the NHMRC recommends consideration of, and US ACIP recommends, immunisation of asymptomatic or mildly symptomatic HIV-infected children with CD4 cell percentage ≥25%.

Travel-specific immunisations

- **Hepatitis A vaccine**: Hepatitis A is a risk for all travellers to developing countries and thus all non-immune HIV-infected travellers to these areas should be vaccinated. The vaccine is safe. An impaired immune response to the vaccine has been demonstrated in HIV-infected persons, with lower seroconversion rates, reduced antibody response and an accelerated loss of antibody. This suboptimal response is more obvious in those with clinical signs of AIDS, with fewer than 65% of people with CD4 lymphocyte count $<200 \times 10^9$/L developing protective antibody levels after a full vaccine course. In cases of advanced immunosuppression, the administration of **immunoglobulin** should be considered if protection against hepatitis A is needed. Pre-vaccination screening for hepatitis A immunity is often worthwhile as previous infection is not uncommon.

- **Typhoid vaccines**: HIV-infected people are at an increased risk of infection, bacteraemia, relapsing disease and persistent infection. The attenuated live oral typhoid vaccine is contraindicated. The injectable Vi polysaccharide typhoid vaccine should be used, and has an effectiveness rate of about 60%, although there is a lower antibody response with CD4 lymphocyte count $<200 \times 10^9$/L. It should be offered to all HIV-infected persons travelling to endemic regions.
- **Yellow fever vaccine**: A live viral vaccine not recommended for those with symptomatic HIV infection or CD4 lymphocyte count of $<200 \times 10^9$/L, due to the theoretical risk for vaccine strain encephalitis or disseminated disease. Such patients should be strongly advised against going to areas of intense yellow fever transmission.

  Asymptomatic HIV-infected persons with a CD4 lymphocyte count $>200 \times 10^9$/L who must travel to areas where risk of yellow fever is high should be vaccinated. In this population no increased incidence of adverse effects has been noted, and the vaccine appears effective. However the vaccine should be given only for the traveller's protection. If vaccine is required for legal purposes only, a letter of exemption from the doctor is generally acceptable (this does not need to state the reason for the exemption). The British HIV association also recommends against vaccination in HIV-positive individuals >65 years due to increasing evidence of an increased risk of adverse events in this age group. We agree with this recommendation although elderly travellers to high-risk endemic regions may be at a greater risk of acquiring yellow fever as a consequence of their travels. In these circumstances advice must be individualised and in consultation with an infectious diseases physician.
- **Japanese encephalitis vaccine** is regarded as safe. Efficacy is reduced, but there is no increase in the incidence of serious allergic reactions to this vaccine.
- **Meningococcal vaccine**: The polysaccharide quadrivalent ACYW conjugate or the A,C,Y,W vaccine may be given if the traveller is entering an area where meningococcal meningitis is epidemic, although an impaired response has been described, particularly against serotype C.
- **Rabies**: As there are uncertainties about the efficacy of rabies post-exposure prophylaxis in HIV-infected persons, a lower threshold should be given to recommending pre-travel rabies vaccination for HIV compared to non-HIV infected travellers to endemic regions. Cell-culture rabies vaccines may be given for pre- or post-exposure prophylaxis, but should be given via the intramuscular route (not intradermal). Due to poor antibody responses to the vaccine in those with significant immunosuppression, those with late-stage HIV disease (CD4 $<200 \times 10^9$/L) who are potentially exposed should receive both immunoglobulin and the full 5-dose course of rabies post-exposure vaccination, even if previously immunised. A protective antibody

Table 7.9.2 Recommendations for routine immunisation of HIV-infected children

	HIV infection	
Vaccine	**Asymptomatic**	**Symptomatic**
DTP	Yes	Yes
OPV	No	No
IPV	Yes	Yes
MMR	Yes	Yes*
H influenzae type b	Yes	Yes
Pneumococcal	Yes	Yes
Influenza	Yes	Yes
Varicella-zoster	Yes	No

* should be considered (see text)

level should be done between days 14 and 28, and if an acceptable level is not achieved (>0.5 IU/mL), an additional dose of vaccine should be given.

- **Cholera**: AIDS patients may have an increased susceptibility to cholera due to reduced gastric acid production, but this has not been confirmed. In addition, there are reports of substantially increased mortality associated with cholera in HIV-infected persons, especially in children under 18 months of age. The oral killed whole cell/B subunit (WC/rBS) cholera vaccine is safe, but the low risk of cholera among travellers argues against its widespread use. The oral live attenuated CVD 103 HgR vaccine is contraindicated in HIV-infected persons.
- **Tuberculosis**: BCG is contraindicated in HIV-positive people, due to the risk of dissemination.

Malaria

There is a significant interaction between malaria and HIV. Recent studies have shown increased risk and severity of parasitaemia and clinical malaria, and reduced response to treatment in HIV-infected people. This is proportional to the degree of immunosuppression. In addition, in HIV-infected pregnant women there is an increased risk of placental malaria, a possibly increased rate of HIV transmission to the fetus, increased pre-term deliveries and low birthweight infants, and post-natal mortality is increased. Finally, persistent malarial infection leads to an increased HIV viral burden, and therefore an accelerated HIV disease progression and facilitated HIV transmission.

Malaria prevention involving anti-mosquito measures (see Chapter 3, Malaria prevention) and chemoprophylaxis are therefore vitally important. However, in

choosing the appropriate medication for chemoprophylaxis, both the resistance patterns of the parasite and the potential interactions with antiviral medications need to be considered.

For chloroquine-resistant malaria, doxycycline, atovaquone–proguanil and mefloquine are acceptable. However, one of the important contraindications to mefloquine is neuropsychiatric disease, which is common in HIV-infected persons, especially if they are taking efavirenz. In addition, mefloquine is metabolised by hepatic p4503A4 enzymes, causing potential drug interactions with antiviral medication (known to decrease levels of ritonavir and possibly other protease inhibitors, and may have reduced levels with nevirapine and efavirenz). Atovaqone–proguanil levels are reduced with ritonavir, lopinavir and indinavir. Doxycycline, in contrast, appears safe in HIV-infected people, without any known interactions with antiviral medications, and therefore we prefer it for HIV-infected persons travelling to chloroquine-resistant areas.

For chloroquine-sensitive areas chloroquine is acceptable, although due to its known immunosuppressive properties it could theoretically affect the host response to infections or could contribute to progression of HIV-related disease. There is no clinical data on this issue. Proguanil is safe although its utility is limited by its increasing lack of effectiveness worldwide.

All the usual recommended standby malarial treatment options can also be used, although medical follow-up post treatment is important due to reported higher treatment failure rates in HIV-infected people. An exception is the use of amodiaquine in people taking efavirenz, which should not be used due to possible increased rates of severe hepatotoxicity.

Travellers' diarrhoea

The principal risk for the HIV-infected traveller is enterically acquired infections. Several pathogens that cause travellers' diarrhoea result in severe, recurrent or persistent disease in HIV-infected persons, and may be associated with extra-intestinal spread. Gastric acid secretory failure is common in patients with AIDS, and mucosal immune function may be impaired in those with a low CD4 lymphocyte count. Thus, a small inoculum of ingested bacteria may produce disease. Great care should be taken to eat and drink safely. Consideration should be given to carrying a portable water filter and/or iodination kit.

HIV-infected persons are at an increased risk of infections due to *Salmonella* spp, *Campylobacter* spp and *Shigella* spp. These are often severe, bacteraemic, difficult to treat, and associated with a chronic relapsing course.

Shellfish should be steamed for 4–6 minutes, thoroughly cooked, or avoided if such preparation cannot be assured. Although this is a general recommendation for all individuals, an increased susceptibility to infection, septicaemia and

death from *Vibrio* spp. makes compliance with this guideline especially important for HIV-infected persons.

Cryptosporidium parvum causes a chronic infection in HIV-infected persons leading to malnutrition, wasting and susceptibility to other infections. Isosporiasis has been associated with malabsorption, weight loss and chronic watery diarrhoea. Both microsporidiosis and *Cyclospora cayetanensis* infection cause chronic diarrhoea in patients with AIDS.

Advise the HIV-infected traveller not to eat uncooked meat, as it may cause toxoplasmosis, and to avoid soft, ripened cheeses, which may carry the *Listeria* bacteria.

Antibiotic prophylaxis may be worth considering for those HIV-infected persons with significant immunosuppression (CD4 lymphocyte $<200 \times 10^9$/L) and those with chronic diarrhoea, who may be more susceptible to complications of superimposed travellers' diarrhoea (such as dehydration and weight loss). In addition it may be worthwhile for short trips (<3 weeks) where the risks of adverse reactions, alteration of faecal flora predisposing to enteric infection, and the selection of resistant organisms are reduced. We recommend a fluoroquinolone with systemic activity like ciprofloxacin in half the treatment dose (see Chapter 4, Travellers' diarrhoea).

Due to the increased severity of enteric infections, prompt treatment should be undertaken for any diarrhoeal illness associated with three or more loose stools within 24 hours, distressing or incapacitating symptoms, fever, or bloody stools. We recommend that an antibiotic treatment course be carried and suggest a fluoroquinolone or azithromycin, as they are the most effective (ciprofloxacin 500 mg twice daily for 3 days or azithromycin 500 mg daily for 3 days). Other drugs such as loperamide (Imodium), diphenoxylate (Lomotil), erythromycin, ampicillin, tinidazole and metronidazole are safe. Medical advice should be sought if symptoms do not settle.

Other infections

- **Acute respiratory infections** are common in travellers, and HIV-infected persons are even more susceptible to infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*, which tend to cause invasive disease and bacteraemia. It is advisable to carry a treatment course of appropriate antibiotics.
- **Tuberculosis** is a major threat to HIV-infected persons, as it has a high risk of progression to active disease. The risk for becoming infected during short-term travel is low, but the probability of exposure increases with longer visits. All HIV-infected persons should have an assessment for tuberculosis infection both prior to and after travel to highly TB endemic areas.

Either the newly-introduced blood test (Quantiferon Gold) or a tuberculin skin test can be used, although the former is more reliable in immunosuppressed persons. Some experts offer prophylaxis (isoniazid 300 mg daily) against tuberculosis to severely immunocompromised patients (with CD4 lymphocyte counts $<200 \times 10^9$/L) intending to travel to endemic areas for more than a few weeks.

- **Leishmaniasis** in HIV-infected persons is often an extensive disease with high mortality. The first manifestation may not appear for many months or years after exposure. The clinical illness may be atypical, serological tests are frequently negative, and the disease may be refractory to treatment. Travellers should be advised to avoid sandfly bites (as well as all other insect bites). Recent reports describe visceral leishmaniasis and Chagas' disease as new opportunistic infections in AIDS patients.
- HIV-infected individuals may also be at increased risk of unusual but severe **fungal infections** after travel to endemic areas; these include coccidioidomycosis, *Penicillium marneffei* and histoplasmosis.
- A number of cases of disseminated **strongyloidiasis** have been reported in AIDS patients. HTLV-1 co-infection should be considered when an HIV-infected person develops disseminated strongloidiasis after travel.
- **Skin and soft tissue infections** may also be a problem for HIV-infected travellers. Pyomyositis from both *Staphylococcus aureus* and *Salmonella* spp. have been described in this population.

Preparation for possible illness

HIV-infected travellers should receive information on how to prevent the more common infections that they may encounter. They should be instructed on possible symptoms, when to seek help, and when and how to self-treat. They should be urged to obtain prompt evaluation of symptoms and early treatment of infection.

It has been found that more than 20% of HIV-infected travellers reported casual sexual activity with new partners while travelling, with 40% not using condoms. Thus safe-sex counselling prior to travel is important, and patients should be advised that infection with additional subtypes of HIV during travel could potentially accelerate the pace of HIV disease progression. They should also be reminded about the risks of other sexually transmitted diseases as well as the risk of transmitting the infection.

Those with advanced HIV infection should know how to access high quality, specialised medical care in the countries they will visit. Where possible, the name, address and phone number of a medical centre or doctor knowledgeable about HIV infection should be given to the traveller. A detailed medical letter outlining their current immune function, health status, medication list and

treating doctor's contact details should also be carried. Finally, ensure adequate supplies of medication are taken or available during the travel, and make the person aware that these may act as a marker of infection and thus require concealment at some border controls.

Where medical evacuation is a possibility, the HIV-infected traveller should have medical insurance that covers such an eventuality arranged prior to travel.

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7.10 The immunocompromised traveller

People with immune compromise represent an important and complex group of travellers for the travel-health practitioner. They have a greater risk of becoming ill with travel-related infections, and the illnesses are often more severe. Vaccinations tend to be less effective or less safe than in the normal host. Nevertheless, with careful education and management, most travel can be undertaken safely, and there are few absolute contraindications to travel. Immunocompromised travellers must be advised about the risks of their particular journey, how infectious risks might be avoided, and when and how to seek help. Each person should be assessed on an individual basis.

Forms of immune compromise

There are many forms of immune compromise, including the use of immunosuppressive medication, malignancy, chronic disease, and congenital immune defects. Others, including HIV, pregnancy, splenectomy, and diabetes have been specifically discussed in other sections of this book. The effect of each on the immune system is different, and thus their implications for pre-travel management will vary.

Immunosuppressive medication

This may include such agents as cyclosporin, tacrolimus, mycophenolate, azathioprine, cyclophosphamide and methotrexate, which significantly weaken the host's immune system. In addition, the newer monoclonal antibody TNF inhibitors such as infliximab and etanercept increase the risk of tuberculosis

and fungal disease. In those receiving corticosteroid doses of >15 mg daily for >2 weeks, live vaccines should be avoided.

Prednisone doses in excess of 20 mg/day (0.3 mg/kg of body weight) can lead to an increased risk of serious infections, with up to eightfold increased risk in persons receiving doses >40 mg/day.

Transplantation

In general, people who have had bone marrow transplantation are more immunosuppressed than those who have had solid organ transplants. Intracellular pathogens such as *Salmonella typhi*, *Listeria monocytogenes*, *Mycobacterium tuberculosis* and fungal infections pose a particular risk, so attention must be paid to education on how to avoid these. Care must also be taken to check that any medication prescribed (e.g. erythromycin) does not interact with the immunosuppressive drugs to increase or decrease their levels. After bone marrow transplantation, the highest risk period for acquisition of an infectious disease is in the first 3 months, suggesting that high-risk travel should be avoided during that period. In addition, individuals should be stabilised on anti-rejection drugs and no longer be transfusion-dependent prior to travel. Haematopoietic stem cell transplant recipients are presumed immunocompetent 2 years after their transplant if they are off immunosuppressive medication and do not have graft versus host disease.

People lose their protective antibodies post haematopoietic stem cell transplants and thus need revaccination (e.g. for tetanus, hepatitis A). If considered necessary and safe (i.e. avoiding live vaccines), ideally, to be effective, the vaccination should not be performed until 12 months after the transplant.

Malignancy and chemotherapy

All forms of malignancy pose an increased risk of infection and a reduced effectiveness of vaccination. These effects are more pronounced for haematological than solid-organ malignancies.

Immunisation

Live vaccines are contraindicated for most immunocompromised travellers, and should be avoided for at least 3 months after completion of cancer chemotherapy. Overall, immunocompromised individuals have weaker and less durable antibody responses than normal individuals.

Specific vaccines

- **Hepatitis A**: The seroconversion rates for the vaccine and the levels of antibody are lower than for normal hosts. In addition, the time to seroconversion is longer and thus if travel is intended soon after initial vaccina-

tion, consideration could be given to providing early protection with immunoglobulin.

- **Hepatitis B**: Increased seroconversion rates can be achieved in immunocompromised individuals by using the high dose vaccine (40 μg/mL).
- **Measles–mumps–rubella**: As this is a live vaccine it should not be given to immunocompromised patients. However, susceptible individuals can be given immunoglobulin as a form of protection if they are travelling to measles-endemic countries.
- **Yellow fever**: Due to the risk of dissemination of the live yellow fever vaccine, it is not recommended for immunocompromised travellers. If travel to yellow fever endemic areas is contemplated, strong advice should be offered against travel. If this advice is not taken, a vaccination waiver letter can be provided explaining why vaccination has not been given. Travelling to an area where yellow fever is active without protection of the vaccine is foolhardy and cannot be sanctioned.
- **Rabies**: As there are uncertainties about the efficacy of rabies post-exposure prophylaxis in immunosuppressed persons, a lower threshold should be given to recommending pre-travel rabies vaccination compared to non-immunosuppressed travellers to endemic regions. Cell-culture rabies vaccines may be given for pre- or post-exposure prophylaxis, but should be given via the intramuscular route (not intradermal). Due to poor antibody responses to the vaccine in those with significant immunosuppression, those who are potentially exposed should receive both immunoglobulin and the full course of rabies post-exposure vaccination (5 doses), even if previously immunised. Serological testing for neutralising antibody level should be done between days 14 and 28, and if an acceptable level is not achieved (>0.5 IU/mL) an additional dose of vaccine should be given. An immunocompromised traveller who sustains animal bites should be referred to an infectious disease physician on return.

Malaria prevention

Give the same advice as for other travellers. However, it is important to check for possible interactions between antimalarial and antirejection drugs (e.g. cyclosporin levels may be increased by mefloquine, chloroquine and doxycycline).

Travellers' diarrhoea

There is an increased risk of bacteraemia during episodes of bacterial gastroenteritis. Ensure particular care is taken in eating and drinking, and advise early use of empiric treatment for diarrhoeal illnesses for these travellers. (See Chapter 4, Travellers' diarrhoea.) It should be cautioned that both azithromycin and doxycycline, which are often recommended in the treatment of travellers' diarrhoea, may increase plasma levels of cyclosporin and tacrolimus.

Table 7.10.1 Vaccines to be avoided in immunocompromised individuals and suitable alternatives

Unsafe vaccines	Alternatives
OPV	IPV
MMR	Immunoglobulin
Oral typhoid	Typhoid Vi
Yellow fever	–
CVD 103HgR cholera	WC/rBS cholera
BCG	–
Varicella	–

Other health hazards

Strongyloidiasis is a serious disease in the immunocompromised person. Emphasise the importance of not walking barefoot, particularly in damp or muddy areas. (See Chapter 5, Non-vaccine-preventable infections.)

Preparation for possible illness

Those with immune compromise should know how to access high quality, specialised medical care in the countries they will visit. A detailed medical letter outlining their current health status, medication list and treating doctor's contact details should also be carried. The traveller should have medical insurance that covers medical evacuation should the need to reach more specialised medical care arise.

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7.11 The splenectomised traveller

Infections and asplenia

The spleen is an important component of our defence against infections. The risk of dying from a severe infection in a person without a functioning spleen varies from eight times higher (an adult who has the spleen removed because of

injury) to 50 times higher (children without spleens) than the general population. Splenectomy has been estimated to carry a lifetime risk of overwhelming sepsis of up to 5%, with the highest risk occurring within the first 2 years after splenectomy, but with up to a third of infections occurring at least 5 years later. Fulminant infections have been reported more than 20 years after splenectomy.

Travellers are prone to sustain cuts, and are at risk from animal bites – common portals for entry of infections. Several of these infections tend to be more severe in those without a functional spleen. Special advice should be given to these individuals.

A medical alert bracelet or card regarding the presence of splenectomy should be carried.

Bacterial infections

Most serious post-splenectomy infections are due to encapsulated bacteria. Pneumococcal infection is the most common and has a mortality of up to 60%. *Haemophilus influenzae* type b infections are less common, but are particularly important in children.

Capnocytophaga canimorsus causes severe infection following bites from dogs and other animals. This infection is particularly severe in asplenic persons. Prophylactic antibiotic treatment is strongly recommended following animal bites. Augmentin (amoxicillin–clavulanic acid) is the drug of choice for non penicillin–allergic persons.

There is an increased risk of bacteraemia from common causes of travellers' diarrhoea such as campylobacter and salmonella.

Antibiotic prophylaxis

Many asplenic people are on long-term antibiotic prophylaxis. Phenoxymethypenicillin (250 mg bd) or amoxycillin 250 mg daily are generally the ones prescribed. Travellers who are not otherwise taking antibiotic prophylaxis should do so during periods of travel.

They should also carry a therapeutic course of antibiotics with them. A supply of amoxycillin (3 grams) or amoxicillin–clavulanic acid should be carried, and the patient educated to take them immediately if they become unwell. (Cefuroxime or moxifloxacin can be used if penicillin allergic). Prompt medical assessment should follow as soon as possible. However, drug-resistant *S pneumoniae* is recognised in North and Latin America, the Asia–Pacific region, Europe, and South Africa. Azithromycin can be offered for initiation of urgent treatment of suspected upper respiratory infections or traveller's diarrhoea. The important message for asplenic individuals is that they must seek medical attention urgently for any fever.

Immunisation

- Asplenia is not a contraindication to vaccination. Live vaccines pose no risk to asplenic individuals, but asplenic individuals respond poorly to polysaccharide vaccines.
- Pneumococcal vaccination is essential. In children the conjugate 13vPCV vaccine should be given followed by the 23vPPV 6–8 weeks later or once the child is 2 years old. In adults the 23vPPV vaccine should be given. Both children and adults should have reimmunisation with the 23vPPV after 5 years. (See chapter 2.11 for more information on pneumococcal vaccination.)
- Meningococcal vaccination is essential: the quadrivalent ACWY conjugate vaccine, **MenACWY-CRM**, known as **Menveo** (Novartis), or Menactra (Sanofi Pasteur), should be given. If not available or appropriate then the conjugate vaccine MenCCV should be given followed by the polysaccharide vaccine 4vMenPV 6–8 weeks later. In this latter situation, a single reimmunisation with 4vMenPV is recommended 3–5 years later. (See chapter 2.9 for more information on meningococcal vaccination.)
- A single dose of *Haemophilus influenzae* type b vaccine is recommended, particularly in young persons. Evidence of benefit is lacking, but no harm is expected.
- Influenza vaccine is highly recommended.
- Varicella vaccine is recommended for the non-immune.

Malaria

The interaction between the spleen and malarial parasites is complex and not clear. Experiments have demonstrated an increased susceptibility and severity of malarial infection in splenectomised *animals*. Anecdotal cases suggest malaria is more severe in certain asplenic individuals. Whether the person is semi-immune or non-immune is likely to be a factor. Delayed clearance of parasitaemia despite appropriate treatment has been found in asplenic individuals.

For asplenic travellers, we would give the best possible antimalarials, and stress the importance of anti-mosquito measures and early medical attention when ill. It may be prudent for the asplenic traveller to avoid areas with highly resistant malaria, especially if mefloquine, doxycycline and Malarone are contraindicated or not tolerated.

Tick bites

Ticks carry many infectious agents (see Table 5.2.2 and Chapter 6). Babesiosis is the most serious infection for the asplenic traveller. This infection is rare and occurs in a few limited regions around the world, including the north-east coast

Specific issues to discuss with asplenic travellers

- Role of spleen in bacterial infections and malaria
- Importance of prompt recognition and treatment of infections
- Animal and tick bites
- Antibiotic prophylaxis
- Carrying a therapeutic course of antibiotics during travel
- Immunisation
- Malaria prevention
- Having a medical alert bracelet, necklace or card

of the United States. Travellers should be advised to seek medical attention early if bitten.

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Chapter 8

Health Issues in Returned Travellers

Chapter outline

This chapter will review some of the health issues to consider in returned travellers. While it does not serve as a comprehensive list of all possible causes of illnesses, it focuses on the more common and/or most important illnesses to consider, the types of presentations expected, and the place of screening of asymptomatic travellers.

All patients should be asked about whether they have travelled recently. This is always important in the assessment of each patient, and has particular relevance in foreign-born patients. A history of travel to developing or tropical countries in the preceding six months is especially important for patients presenting with fever or other symptoms suggestive of an infection.

8.1 Infections in travellers

With increasing complexity of travel itineraries, increasing frequency of international travel to tropical regions, and increasing numbers of travellers among high-risk groups, such as those with immunosuppression, the elderly, pregnant women and young children, medical practitioners are more often being required to manage travel-related illness. General data are lacking regarding the spectrum of illnesses and the frequency of presentations to general practitioners by Australian returned travellers, but is is estimated that up to one in five travellers seek medical consultation from a general practitioner after returning from abroad. Many ill returned travellers will need to be referred for a specialist opinion, although the urgency of referral varies according to the diagnoses being considered.

The most common infections in returned travellers affect the gastrointestinal and respiratory tracts, followed by cutaneous and sexually transmitted infections. The most common potentially life-threatening travel-related infection is malaria, particularly falcipurum malaria, which can progress rapidly unless appropriate treatment is given early; malaria must therefore be excluded in all patients who present unwell after returning from a malaria-endemic area.

Some less common imported infections may have an importance out of proportion to their incidence because of the need for urgent intervention (e.g. meningococcus), or because of their transmissibility and consequent public health implications (e.g. viral haemorrhagic fevers, measles). Consequently, travellers – and especially those with a fever – need immediate attention to rule out serious and potentially life-threatening conditions.

Knowledge of the incubation period of particular infections is important. However, many illnesses acquired by travellers will be unrelated to travel or will be due to routine cosmopolitan infections acquired during travel rather than an 'exotic' cause. Therefore, assuming all infections occurring after travel abroad are caused by exotic pathogens is inappropriate and may lead to errors just as serious as those related to ignorance of possible travel-related conditions. Additionally, travellers may return with 'routine' infections (such as urinary tract infctions) that are due to multi-resistant organisms, and this needs to be considered in the choice of empiric antibiotic therapy.

Frequency of illness among travellers

An illness is reported in at least 50% of travellers to developing countries. The probability of infection is related to a number of factors, including:

- destination(s)
- duration of travel
- reason for travel (e.g. business versus visiting friends and relatives)
- season
- type of travel (e.g. backpacking versus five-star accommodation, rural versus urban areas)
- behaviour
- specific prophylactic measures such as immunisation and malaria chemoprophylaxis
- individual susceptibility.

It is difficult to determine accurately the actual risks of different infections during travel according to specific itinerary chracteristics. However Table 8.1.1 shows the kinds of infections seen in returned travellers, and Table 8.1.2 shows estimates of illness incidence among European and North American travellers to the tropics.

Table 8.1.1 Reason for seeking medical care among Australian and multinational travellers with febrile illnesses acquired overseas

Diagnosis	Percentage of diagnoses (n = 624) [O'Brien]*	Percentage of diagnoses (n = 24 920) [Wilson]#
Malaria	27	21
Respiratory illness	16	14
(Bacterial pneumonia)	(4)	(1)
(Influenza)	(4)	(1)
Gastrointestinal illness	12	15
Dengue fever	7	6
Typhoid/paratyphoid (enteric) fever	4	2
Rickettsial infection	3	2
Hepatitis A	1	<1
Fever, no diagnosis	7	22

* O'Brien (2006)
# Wilson, Weld et al. (2007)

It is also important to remember that the frequency of acquiring certain illnesses during a trip may not correspond to the frequency of presentation with those illnesses following return. For example, data on diarrhoeal illness among studies that evaluate illness occurring during travel show a predominance of bacterial causes of diarrhoea. However among patients seen after travel, diarrhoea caused by parasites predominates. This is because, if the symptoms persist on return, they are usually more chronic in nature, and chronic diarrhoea is usually due to different organisms than acute bouts of travellers' diarrhoea that have resolved spontaneously.

History and physical examination

It is essential to take a detailed travel history as this will help to estimate the relative likelihood of potential causative aetiologies.

Duration of travel

For many illnesses that occur in travellers, short at-risk exposure periods (even <24 hours) may be sufficient to acquire illness, although increasing travel duration is associated with increased risk of infection. For example, travellers' diarrhoea, malaria, hepatitis A, dengue and enteric (typhoid/paratyphoid) fever can be acquired following journeys with travel durations as short as one or two days. By contrast, there are some diseases that occur almost exclusively after prolonged or repeated exposures and are therefore rarely seen in short-term travellers. These include filariasis, tuberculosis, and leprosy. Many of these infections have long periods of latency and may not present for years after travel.

Table 8.1.2 Estimates of incidence of health problems per 100 000 European and North American travellers to the tropics per month

Any health problem	45 000
Travellers' diarrhoea (30–80%)	35 000
Consulted doctor abroad or back home	8 000
Malaria (no prophylaxis to West Africa)	2 000
Acute febrile respiratory infection	1 400
Influenza A or B	1 000
Giardiasis	700
Injury	500
Hepatitis (all types)	450
Amoebiasis	400
Tuberculosis	350
Hepatitis A (300–2000)	300
Dengue (South-East Asia)	200
Animal bite with rabies risk	200
Gonorrhoea	200
Malaria (all travellers)	< 100
Hepatitis B (80–240)	85
Syphilis	40
Shigellosis	20
Typhoid (3–30)	12
HIV infection	10
Cholera	0.3
Meningococcal disease	0.07

Adapted from Steffen (1987) and Hill (2000).

Precise travel itinerary

Knowing the exact destinations a traveller has visited is critical to compiling an accurate differential diagnosis. Countries vary greatly in disease patterns – for example, yellow fever occurs only in Africa and Latin America, and Japanese encephalitis is confined to parts of Asia. Even within countries there can be focal differences in disease risks according to level of urbanisation, climate, altitude, and other factors. For example, malaria in Thailand occurs only in rural areas bordering Cambodia, Laos and Myanmar, but not in Bangkok or in major tourist resorts such as Phuket or Koh Samui. In Indonesia it is common in

eastern parts of the country, especially West Irian, but it is rare in Bali. Season of visit is also important in assessing risk.

Type of exposures

This includes information about the type of travel undertaken (e.g. backpacking versus business tour) and the quality of the accommodation (e.g. five-star hotel versus hostel/family residence). Knowledge of specific activities undertaken is also important, as this may imply specific risk exposures. For example, the types of food eaten, sexual behaviour, animals encountered, recreational and occupational exposures, and contact with insect vectors may be clues to the possible diagnoses (See Tables 5.2.1–5.2.4 in Chapter 5, Non-vaccine-preventable infections).

Vaccination history

The protective efficacy of immunisations varies considerably and also depends on time since the last dose. A history of up-to-date immunisation with highly efficacious vaccines such as yellow fever, rabies, tetanus, hepatitis A and hepatitis B makes these diagnoses less likely. This is not true for less effective vaccines such as typhoid (approximately 70% effective) and BCG.

Medications

Both routine drugs and medications given specifically for the trip may profoundly affect illness. Prophylactic medications may reduce the risk of some infections. In many developing countries a wide variety of potentially toxic drugs are available over the counter. Travellers often self-medicate with antibiotics, which may modify symptoms and laboratory results without effecting a cure, or may themselves cause fever and other symptoms.

Chronology of symptoms

When assessing potential causes of illness, it is crucial to know the duration of travel, the time interval between the patient leaving an endemic area and the onset of illness, and the incubation periods of relevant infections. This may allow exclusion of many possibilities without extensive investigations. For example, an incubation period of three weeks or more excludes many arboviruses, such as dengue, and viral haemorrhagic fevers. Most travellers present soon after arrival home, with over 90% of infections related to short-term travel manifesting within six months of return. It is rare for illness related to short-term travel to develop more than one year later, so a history of recent travel is more likely to be relevant in defining the cause of acute illness than is remote travel. However, history of travel to a malarious area is always relevant.

Medical history

The risk or severity of illness may be influenced by underlying medical conditions (e.g. malaria is more severe in pregnancy or splenectomised individuals,

those on immunosuppressive medication are more likely to develop tuberculosis) or previous exposure (prior hepatitis A provides life-long immunity).

Physical examination

Often, distinctive physical findings will be lacking in returned travellers. However, some findings may increase or decrease the likelihood of certain travel-acquired diseases. For example, the presence of a rash makes the diagnosis of malaria less likely, but makes dengue, acute HIV, rickettsial infections and leptospirosis more likely. Hepatomegaly (with or without splenomegaly or jaundice) may be found in conditions such as malaria, viral hepatitis, amoebic liver abscess, enteric fever or brucellosis.

Evaluation of infections in returned travellers

The approach to assessing the traveller who returns home unwell should make use of signs, symptoms, itinerary details and epidemiology (as outlined above).

If the traveller is unwell, the conditions with the potential for the greatest morbidity and mortality need to be considered and excluded first. For example, if the patient has a fever, the possibility of malaria or septicaemia (e.g. due to typhoid/paratyphoid, meningococcal or pneumococcal sepsis) needs to be assessed immediately.

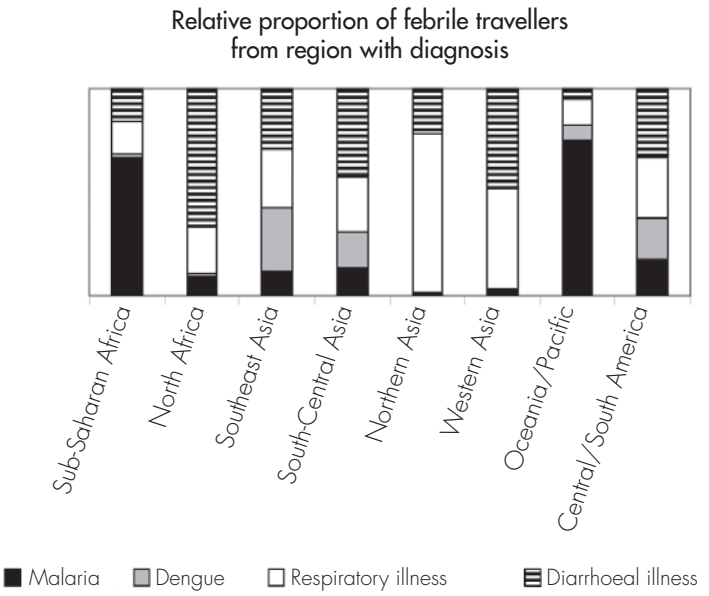
8.2 Clinical syndromes

Fever

The clinical approach to a febrile traveller is in many ways similar to that for any febrile patient. Appropriate steps include assessing the severity and looking for localising symptoms or signs. However, a travel history should lower the threshold for intervention because of the additional possibility of 'exotic' infections. If the traveller has been to a malaria-endemic area, this needs to be considered and excluded promptly with appropriate testing. Blood cultures to diagnose enteric fever and other causes of septicaemia should also be taken immediately. Blood for initial serology for dengue fever and rickettsial infections should also be collected at the time of presentation, and again 2 to 4 weeks later to determine whether or not seroconversion has occurred, confirming recent infection. Most febrile travellers should be hospitalised.

In attempting to diagnose the cause of the fever, it is important to consider that the most common causes of a febrile illness in returned travellers include malaria, gastroenteritis, upper respiratory tract infections, dengue fever, bacterial pneumonia, influenza, enteric fever, hepatitis A and rickettsial infections (Table 8.1.1 above, Figure 8.2.1). Together, these aetiologies account for over 80% of the cases.

Figure 8.2.1 Cause of fever according to region of travel



Adapted from Wilson, Weld et al. (2007).

Fever in a previously healthy young or middle-aged person after travel is most likely to be travel-related. In older individuals, causes unrelated to travel (such as urinary tract infection, pneumonia, and intra-abdominal sepsis) become increasingly likely. These infections may be due to highly resistant pathogens, especially if they occur in the first few weeks after travel. In particular, there is a high chance of having an infection caused by a multi-resistant Gram-negative bacterium in travellers returning from South-East Asia.

In addition to these clinical clues, it is useful to categorise the fever as acute (<10 days), intermediate (10–21 days) or chronic (>21 days), and to assess the likely incubation period (Table 8.2.1).

Table 8.2.1 Incubation periods of imported infections

Less than 10 days	Intermediate (up to 21 days)	Greater than 21 days
Dengue	Malaria	Malaria
Influenza	Viral haemorrhagic fever	Viral hepatitis
Yellow fever	Rickettsial disease/Q fever	HIV
Chikungunya	African trypanosomiasis	Rabies
Plague	Typhoid fever	Visceral leishmaniasis
Paratyphoid fevers	Brucellosis	Amoebic liver abscess
Legionella	Leptospirosis	Filariasis
	Relapsing fever	Tuberculosis
		Q fever
		Acute schistosomiasis

Some important diagnoses in febrile returned travellers

Malaria

Malaria can mimic other illnesses clinically and may be rapidly fatal if undiagnosed. Essentially any fever in a patient returning from a malaria-endemic area should be considered to be malaria until proven otherwise. The shortest incubation period for malaria is 7–10 days, but presentation can be delayed, particularly in travellers who were taking chemoprophylaxis. For travellers infected with *P vivax* malaria it is not unusual for the onset of symptoms to be delayed for more than 1 year. It must be remembered that semi-immune travellers from a malarious area may not be unwell and febrile or may have an additional cause for their fever even if malaria parasites are found in their blood.

Enteric fever

Enteric fever is caused by infection with *Salmonella typhi* or *Salmonella paratyphi*. The incubation period is 5–21 days. The common destinations of acquisition include South-East Asia (particularly Indonesia), South Asia (especially India), Africa, Latin America, and the Middle East.

Enteric fever usually presents nonspecifically in the early stage with fever, headache, malaise, anorexia, abdominal pain, and non-productive cough. Constipation is more common than diarrhoea in adults. Serious complications include intestinal bleeding/perforation and septic shock. Blood cultures and stool cultures are successful in establishing the diagnosis of enteric fever in the vast majority of travellers. Without treatment, the fatality rate is 10–30%, although death in returned travellers is unusual, probably because travellers present to medical practitioners at a relatively early stage of infection. Treatment is usually with a quinolone antibiotic such as ciprofloxacin, but there is increasing resistance to quinolones, especially in isolates from the Indian subcontinent. Alternatives include oral azithromycin or intravenous ceftriaxone.

Viral haemorrhagic fevers (VHF)

Although uncommon, it is important to consider the possibility of VHF in returned travellers because of the potential public health consequences and the high infectivity of blood, urine and respiratory secretions. The VHFs include Lassa fever, Ebola and Marburg viruses, Congo–Crimean haemorrhagic fever, Rift Valley fever, and yellow fever. Clues on history that may suggest their presence include presentation with fever within three weeks of exposure, especially if there has been direct contact with blood, body fluids, secretions or excretions of a person or animal with VHF. Clinical findings suggestive of VHF include fever, malaise and myalgia, especially if there are haemorrhagic manifestations in skin, mucous membranes or internal organs, or signs of hypotension and shock (present late in disease). If VHF is suspected, immediate hospitalisation

and rapid notification to the communicable disease unit of the local health department are required.

Dengue fever and Chikungunya virus

These are discussed in more detail in Chapter 5. Both have a short incubation period (usually <5 days for Chikungunya and <14 days for dengue fever), and both can cause symptoms including fever, mylagias/arthralgias, and often a rash. The two illnesses can sometimes be difficult to distinguish clinically.

Rickettsial infections

These are also discussed in more detail in Chapter 5. Rickettsial infections are comprised of the spotted fever, typhus and scrub typhus groups. Different species occur in different geographic regions, and result in illness that is often characterised by fever and rash.

Diarrhoea

See Chapter 4, Travellers' diarrhoea.

Diarrhoea is the most common illness that occurs in travellers. The incidence averages 50% (range: 30–80%) during the first 2 weeks of travel to developing countries. Causes include bacteria, viruses, parasites and toxins. About 10–20% of diarrhoea involves more than one pathogen, and several discrete episodes of diarrhoea in the same patient may be caused by multiple organisms with different incubation periods acquired during the same contaminated meal.

Acute diarrhoea (≤2 weeks)

Most travellers' diarrhoea is brief, self-limited, typically non-inflammatory in type, and will have settled by the time of return. The mean duration of symptoms is 4 days; fever and/or bloody diarrhoea occur in 10–20% of cases. Although a wide range of pathogens are implicated, enterotoxigenic *E coli* (ETEC) is the most frequent, being found in 40–70% of cases when a specific diagnosis is made. The onset of bacterial diarrhoea is usually abrupt. Other commonly identified pathogens include *Shigella* spp., *Salmonella* spp., *Campylobacter jejuni*, *Yersinia* spp., *Vibrio parahaemolyticus*, *Aeromonas* spp., rotavirus and Norwalk-like virus. Remember also that patients with malaria can sometimes present with diarrhoea.

Chronic diarrhoea (>2 weeks)

When diarrhoea persists beyond 14 days a wider spectrum of causes needs to be considered. Although a bacterial aetiology may still occur, non-ETEC bacteria are likely to be involved. *Giardia lamblia* is the single most common agent causing chronic diarrhoea. Other causes include *Entamoeba histolytica*, *Cyclospora cayetanensis*, *Cryptosporidium* and *Isospora belli*. Some helminth infections may

also be associated with chronic gastrointestinal symptoms, including hookworm, *Ascaris lumbricoides*, *Trichuris trichiura* (whipworm), and *Strongyloides stercoralis*. Patients with chronic diarrhoea after travel should have their faeces sent for microsopy, culture and parasite examination. Even if no pathogen is demonstrated (including no demonstration of *Giardia*), all patients with chronic post-travel diarrhoea deserve an empiric trial of therapy for giardiasis. We typically recommend a stat dose of 2 g tinidazole (fasigyn) (50 mg/kg for children).

Non-infectious causes

Travellers' diarrhoea may exacerbate or precipitate symptoms of irritable bowel syndrome or inflammatory bowel disease in the absence of continuing infection. A common diagnosis in returned travellers with persisting gastrointestinal symptoms is 'post-infective irritable bowel syndrome'. No specific therapy is of proven benefit in these cases, although increasing fibre and reducing intake of dairy products and alcohol are often helpful.

Respiratory infections

Respiratory symptoms are reported by up to 30% of travellers. Respiratory infections are generally considered to be the second most common cause of illness in travellers after travellers' diarrhoea. Some emerging evidence suggests that travel to Asia is associated with an increased risk of acquiring a respiratory infection.

Many respiratory infections acquired by travellers are caused by common pathogens such as the common cold, influenza, or streptococcal pharyngitis. In one study, influenza occurred in almost 3% of travellers. It should be remembered that, while specific influenza seasons occur in the northern (November–March) and southern hemispheres (April–September), influenza is a year-round disease in the tropics. Seasonal influenza can be imported 'out-of-season' by travellers, and travel is expected to be an important aspect of spread should an influenza pandemic or avian influenza outbreak occur. Consequently, returned travellers who are unwell with suspected influenza should be isolated and, if admitted to hospital, careful contact and respiratory precautions should be upheld.

It is well accepted that travel played a vital role in the rapid spread of SARS (severe acute respiratory syndrome). Although no community-acquired cases have been reported since 2002, it is possible that new cases could emerge in the future (see Chapter 5, Non-vaccine-preventable infections). Travel also played an important role in the spread of pandemic influenza A (H1N1) 2009 ('swine flu').

Legionnaires' disease is also common in travellers, particularly to parts of Europe, and may be associated with hotels or spas. Travellers going on cruise ships are also at greater risk of both influenza and legionella infections.

Travellers to Saudi Arabia for the Hajj are at extraordinarily high risk of respiratory infections, probably related to the very high level of crowding, which facilitates transmission of respiratory pathogens.

Occasionally respiratory symptoms are due to 'exotic infections', such as acute schistosomiasis (Katayama fever), the migratory phase of Ascaris, strongyloides or and hookworm infection, acute histoplasmosis, tularaemia and plague. It must also be remembered that both malaria and typhoid can present as fever and cough.

Skin problems

Skin problems occur commonly following travel. The most frequently encountered problems related to travel are sunburn, urticaria, insect bites, swimmer's itch, seabathers eruption, cutaneous larva migrans, and myiasis/tungiasis. Additionally, some skin problems such as cellulitis and bacterial abscesses occur more commonly in tropical than temperate regions. Spider bites and envenomations may also occur.

Swimmer's itch is a dermatitis that develops on exposed areas of the skin after contact with waters infested with larval forms of avian schistosomes, and if required can be managed symptomatically with topical antipruritic and antihistamine medications. By contrast, seabathers eruption is a dermatitis that appears on covered areas of the skin and is caused by anemone or jellyfish larvae, which typically become trapped underneath bathing suits. Cutaneous larva migrans, also known as creeping eruption, is typically caused by animal hookworm larvae which make contact with human skin during sunbathing (Chapter 5). Myiasis and tungiasis are due to infestation of the skin by fly larvae (Chapter 5).

Some systemic infections are also commonly associated with skin changes, such as dengue, rickettsia, acute HIV, leptospirosis, viral haemorrhagic fevers, and meningococcaemia. In addition, non-immune travellers may be at increased risk of acquiring measles and rubella when they travel to countries where childhood immunisation rates are lower than in Australia, which includes many European countries. If measles is suspected in a returned traveller, public health authorities should be notified rapidly.

Neurological infections

There are a number of important travel-related causes of selected neurological syndromes. Cerebral malaria due to *Plasmodium falciparum* can cause encephalopathy and coma. Acute meningitis can occur in travellers, and may be due to meningococcal infection. Although this is seen rarely in returned travellers, epidemics occur in many countries in Africa, and this infection may also occur in travellers who have visited Saudia Arabia during the Hajj. Acute meningitis may also be due to Lyme disease (caused by *Borrelia burgdorferi*), and has been seen in returned travellers from North America and Europe. Lyme disease can also be the cause of other neurological syndromes.

Chronic meningitis can be caused by tuberculosis or occasionally by brucellosis. HIV and syphilis should also be considered as a cause of meningitis in travellers

with a history of unsafe sexual exposures. Eosinophilic meningitis may be caused by certain parasitic infections, including *Angiostrongylus cantonensis*, *Gnathostoma spinigerum*, and *Schistosoma* spp. Encephalitis in returned travellers may be due to Japanese encephalitis or other arboviral encephalitides, rabies, or African trypanosomiasis (see Chapter 5). Ciguatera and other seafood toxins can also cause neurological presentations.

Hepatitis

The most common form of hepatitis acquired by travellers is hepatitis A, which is contracted via exposure to contaminated food or water. It is estimated that unvaccinated travellers to the tropics develop hepatitis A at a rate of 3 to 20 per 1000 persons per month, but the risk can be almost eliminated by vaccination.

Another virus transmitted via the faecal–oral route that also causes sporadic hepatitis in travellers is hepatitis E. Like hepatitis A, hepatitis E is generally associated with a relatively benign clinical course. However, contracting hepatitis E during the third timester of pregnancy is associated with up to 20% mortality of the mother.

The prevalence of hepatitis B is as high as 15% in some areas, including parts of South-East Asia, China, Africa, Pacific Islands and the Amazon basin. Overall hepatitis B is three to five times less common than hepatitis A among travellers, but both account for similar mortality. Behaviours involving hepatitis B risk are widespread among travellers. Expatriates, healthcare professionals, and individuals who have unprotected sexual contacts, share needles, access healthcare services, or engage in activities with a high injury risk in endemic areas are at greatest identifiable risk.

Hepatitis C is a rare infection among returned travellers, but parenteral exposure can occur in areas with a high prevalence of infection, such as Japan, Mediterranean countries, the Middle East and Africa.

A number of other infections can cause hepatitis with or without jaundice, often as part of a systemic illness. These include dengue, yellow fever, malaria, Q fever, amoebic liver abscess, and leptospirosis. Some viral causes, particularly the haemorrhagic fever viruses, have limited geographic distribution and, although uncommon in travellers, need to be considered if there is an appropriate exposure history. In addition, drugs that travellers may be taking can be associated with hepatic inflammation.

8.3 Screening the returned traveller who is well

A question that commonly arises is whether or not well travellers should be screened.

It is unnecessary to screen asymptomatic short-term travellers who have not experienced any health problems or have only had trivial self-limited problems such as diarrhoea, as there is no proven benefit of screening these travellers.

For the 'worried well' traveller who has a history of certain high-risk exposures, targeted screening can be considered. For example, individuals who have swum in freshwater lakes known to be infested with schistosomiasis should have serology and urine/faeces for parasite examinations taken (see Chapter 5). For travellers who have had unprotected sex while away, it is appropriate to screen for STIs. Relevant screening tests would include swabs from any site with a discharge, urine PCR for chlamydia and gonorrhoea, and serology for hepatitis B, syphilis, and HIV. However, knowledge of the pre-patent period (time from infection until a laboratory diagnosis can be made) is required in order to be able to rule out the presence of subclinical disease. As examples, the pre-patent period for schistosomiasis would be a minimum of 2 months, and for HIV about 4–6 weeks.

For longer term travellers or expatriates, a medical examination is advisable and it may be appropriate to screen for possible latent infections that may reactivate in the future, such as tuberculosis, strongyloidiasis, or chronic asymptomatic infections (e.g. HIV).

Initial laboratory tests to consider in the unwell/febrile traveller

- FBE, LFTs, inflammatory markers
- Microscopy and cultures (including examination for ova and parasites): blood, urine, sputum, stool
- Thick and thin smear/ICT test for malaria (three tests should be performed, usually on consecutive days
- Serology: schistosomiasis, strongyloides, hepatitis, HIV, arboviral, rickettsial, other
- CXR (+/– other imaging).

Issues to consider in the unwell returned traveller

- Could this be a life-threatening infection? The two diagnoses specifically related to travel that are seen most frequently and need urgent consideration and exclusion are malaria and enteric fever.
- Could it be one of the less common illnesses, but potentially fatal if missed and curable if found? These should always be thought of, e.g. meningococcus, legionella, amoebae, melioidosis.

Important diagnoses to consider in the unwell returned traveller

Fever plus rash

- Dengue fever, Chikungunya, rickettsia, leptospirosis
- Meningococcus, gonococcus, syphilis
- HIV, EBV, CMV, measles
- Malaria less likely

Fever plus diarrhoea

- Travellers' diarrhoea, malaria, typhoid/paratyphoid

Fever plus respiratory symptoms

- Influenza, common cold, streptococcal pharyngitis/pneumonia, Legionnaires' disease, mycoplasma, Q fever
- 'Exotics': tuberculosis, melioidosis and paragonimiasis
- Infiltrates (transient): acute schistosomiasis (Katayama fever), migratory phase of ascaris, strongyloides or hookworm infection, acute histoplasmosis

Fever plus neurological symptoms

- Cerebral malaria
- Meningococcal meningitis
- Tuberculous meningitis
- Other exotics: Lyme disease, leptospirosis, brucellosis, melioidosis, cysticercosis, schistosomiasis, *Angiostrongylus cantonensis*, *Gnathostoma spinigerum*
- Encephalitis: Japanese encephalitis, other arboviral encephalitis, African trypanosomiasis, rabies, neurosyphilis, HTLV-1 infection

Fever plus jaundice

- Hepatitis A/B/C/E
- Malaria
- Yellow fever, dengue
- Amoebic liver abscess
- Q fever, rickettsia, leptospirosis

Fever and lymphadenopathy

- Rickettsia
- TB
- Syphilis
- Filariasis
- African trypanosomiasis
- Tularaemia

- Is this an uncommon disease but one of public health importance? This includes such illnesses as measles, tuberculosis and viral haemorrhagic fevers.
- Could the fever have subsided, but the disease still be present? If not considered, these illnesses will often be overlooked, e.g. acute HIV, schistosomiasis (Katayama fever).
- Could this be an emerging pathogen? As new infections are constantly appearing worldwide, this should always be considered, e.g. SARS.
- Many illnesses acquired by travellers will be unrelated to travel.
- Gastrointestinal and respiratory infections are the most common infections in returned travellers.
- Some imported infections have an importance out of proportion to their incidence because of the need for urgent intervention (e.g. malaria, enteric fever), or because of their transmissibility (e.g. viral haemorrhagic fevers, measles).
- Fever in a returned traveller from malaria-endemic areas must always be assumed to be due to malaria until proven otherwise.
- Accurate patient assessment requires a comprehensive travel history encompassing the exact itinerary, mode of travel, patient characteristics, behaviour, and immunisations.

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Chapter 9

Resources for Travel Health Information

Chapter outline

Although we have tried to include in this manual the key information to support doctors in advising travellers, a single printed book cannot provide absolutely everything relevant to the subject. Users of the manual may from time to time need greater depth and detail than a small book can provide. In addition, although the principles of good travel medicine remain largely unchanged over time, the actual degree and distribution of health risks to travellers change rapidly, and travel doctors will need rapid access to high quality, up-to-the-minute information about current disease risks. The tools available to address these risks and recommendations for their use also change. Further, modern travellers will often wish to be proactive in safeguarding their health, and will sometimes ask their medical advisers to recommend books or other resources they can take with them and/or consult as needed. Many travellers will have visited a number of internet sites before their pre-travel consultation, and may even come armed with printouts and detailed questions. The role of the travel medicine adviser then includes ensuring that these 'well informed' travellers actually understand what they have read and have a realistic appreciation of the various health risks. These travellers sometimes need perspective and appropriate priorities more than they need information *per se*.

This chapter is therefore presented in four sections: a listing of authoritative sources offering greater depth and detail for the travel doctor who wants to go into a subject in more detail, or who needs to answer a specific detailed question; directions to credible sources (including the World Health Organization and the US Centers for Disease Control and Prevention) that offer the latest information on the current distribution of health risks such as malaria; pointers towards some resources that may be useful for the traveller who wants reference

material on the journey; and some other resources of general use. There is of course some overlap between these categories.

The distinction between print and electronic resources has become completely blurred since the last edition of this manual. Many hard-copy books can also be downloaded directly from the internet as PDF files (see <www.adobe.com> for a free reader for these files), and many books come with CDs of images and/or links to updates on the publisher's website. Copying out URLs is tedious but can be rewarding, especially if you create bookmarks in your web browser so you can easily revisit useful sites.

9.1 Resources offering greater depth and detail

International Travel and Health (2011). World Health Organization: Geneva. ISBN-13: 9789241580465 and ISBN-10: 9241580461. This book, updated annually, aims to present the situation 'as on 1 January each year', but the website also has links to newer material including updates for travellers, disease distribution maps, and an interactive map detailing disease risks for each country. The website <www.who.int/ith/en> is well worth bookmarking in your web browser for quick access. The 2011 edition has 250 pages; the price is 30.00 Swiss francs or US$36.00 for the hard copy via the website, but the whole book can be downloaded for 10.00 Swiss francs or US$12.00 as a pdf (ISBN-13: 9789240686434) or ebook (ISBN-13: 9789240686472 and ISBN-10: 9240686479).

WHO also maintains a website that monitors vaccination activities in member countries. The 'country profile' for each country includes its current recommended vaccination schedule. Find it at <http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm>.

The Australian Immunisation Handbook (2008) 9th edition. National Health & Medical Research Council, Canberra. ISBN 1-74186-483-6. This handbook contains the official Australian recommendations, based on review of evidence and expert opinion. It is updated every few years in hard copy, but interim revisions to some chapters appear on the website, which is therefore more up-to-date. The latest version can be found on line at <www.health.gov.au/internet/immunise/publishing.nsf/content/handbook-home> and a hard copy can be requested by email via Handbook@health.gov.au. The handbook includes a specific, although brief, chapter on vaccinations for travellers <www.health.gov.au/internet/immunise/publishing.nsf/content/handbook-travel>, though this is not necessarily the best chapter in the handbook.

CDC Health Information for International Travel 2012 (2012). Brunette GW (ed.). Oxford University Press, New York: ISBN: 978-0-19-976901-8. This is the current 'yellow book', updated every two years in hard copy and more

frequently online. In most areas CDC recommendations are justifiably highly regarded. This book tends to have more detail on specific diseases than the World Health Organization (WHO) publication, and the recommendations tend to be practical, detailed, well considered, and based on a comprehensive and referenced assessment of available evidence. The online version has useful hyperlinks between relevant sections and is available at <wwwnc.cdc.gov/travel/page/yellowbook-2012-home.htm>. The same page has a link to Oxford University Press, the distributor, for online ordering of the 640-page hard copy version, at $US45.

The main CDC website at <www.cdc.gov/travel/yb/index.htm> has links to much useful travel health information, including an interactive malaria map application at <http://cdc-malaria.ncsa.uiuc.edu>. You can search for a city, province or country, or just click on the main map for a tabular summary of malaria distribution and suggested chemoprophylaxis.

Manual of Travel Medicine and Health (2007). Steffen R, DuPont HL, Wilder-Smith A. 3rd edition. Decker: Hamilton, Ontario. This is the shorter, cheaper, more practically oriented (though not fully referenced) and more up-to-date companion to the textbook below. It is excellent. CDs are included.

Textbook of Travel Medicine and Health (2001). DuPont, HL, Steffen R. 2nd edition. ISBN 1-55009-037-9. Decker: Hamilton, Ontario. The purchase price includes a CD with the full text. This has always been more a source of comprehensive background material than a ready reference, and is now ageing somewhat.

Travel Medicine (2004). Keystone JS, Kozarsky PE, Freedman DO, Nothdurft HD, Connor BA (eds). Mosby: Edinburgh. Although no longer new, this text is excellent and an alternative to DuPont and Steffen's textbook, with more pictures and colour. It aims both to be a 'how to' book and to constitute a complete course in travel medicine. A CD and access to a searchable online version are included.

Vaccines – Expert Consult (2008) Plotkin SA, Orenstein WA, Offit PA (eds). 5th edition. Elsevier-Saunders: Philadelphia. ISBN 978-1-4160-3611-1. This is the magnum opus on vaccines and the key reference work. It is large (1748 pages, with 600 illustrations), and expensive.

Travellers' Malaria (2007) Schlagenhauf-Lawlor P. 2nd edition. Decker: Hamilton, Ontario. ISBN-10: 1550093363 and ISBN-13: 978-1550093360. This is a big (408 page) well-written, detailed and authoritative reference for those with a special interest in malaria.

Travellers' Diarrhea (2008). Ericsson CD, DuPont HL, Steffen R. 2nd edition. Decker: Hamilton, Ontario. ISBN 978-1-55009-371-1. This is an up-to-date text on the pathogenesis and state-of-the-art management of travellers' diarrhea.

The Travel & Tropical Medicine Manual (2008). Jong EC, Sandford C (eds), 4th edition. Saunders: Philadelphia. ISBN 9781416026136. This is a useful reference, but despite a claim to wider readership it is more directed at doctors and is more expensive than Dawood's *Travellers' Health* (see below). It tends to a US orientation.

Control of Communicable Diseases Manual (2008). Heymann D (ed.). 19th edition. American Public Health Association: Washington DC. ISBN 978-0-87533-189-2. This is a standard reference, covering epidemiological information, public health issues and control measures for a comprehensive range of infectious diseases. It is especially useful for those with public health responsibilities. In 2010 Unbound Medicine Inc <www.unboundmedicine.com/store/communicable_diseases> produced a version for mobile phones and the web – bringing it back closer to the handy pocket reference it was before it grew to 746 pages.

PDQ Traveler's Malaria (2005). Schlagenhauf P, Funk-Baumann M. Decker: Hamilton, Ontario. ISBN-10: 155009324X and ISBN-13: 978-1550093247. This is one of the PDQ – as in 'Pretty Darned Quick' – series, medium-sized (210 pages) and paperback. A CD is included. It contains easy-to-read malaria maps, which are not detailed but are nevertheless an excellent source of quickly accessable information on malaria risk by country.

A short paper published in *Nature* in 2008 – and cited more than 350 times by the time of writing – provides some fascinating insights into the changing global patterns of emerging infectious diseases. See Jones KE, Patel NG, Levy MA, Storeygard A, et al. Global trends in emerging infectious diseases. Nature 2008 Feb 21; 451(7181):990–3.

The Pan-American Health Organization (PAHO – the WHO regional organisation for the Americas), offers good maps and statistics about infections throughout Latin America, including dengue and malaria, at <http://new.paho.org/hq/index.php?lang=en>. From this home page click on 'Projects and Programs' and look for dengue, malaria and others under 'Health Surveillance and Disease Prevention and Control'.

The Public Health Agency of Canada offers information for travel medicine professionals at <www.phac-aspc.gc.ca/tmp-pmv/prof-eng.php>. (There is a related site for the public – see below.)

The Canadian Committee to Advise on Tropical Medicine and Travel (CATMAT) provides guidelines, statements and recommendations at <www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv>.

The Travel Medicine Division of the Scottish Centre for Infection and Environmental Health maintains the 'Fit for travel' site at <www.fitfortravel.scot.nhs.uk/home.aspx>.

The multinational Malaria Atlas Project <www.map.ox.ac.uk> offers useful maps of malaria distribution at global, regional and country level. Click on 'Data' on the main menu for access to these maps.

The WHO Global Atlas website offers a range of maps and data queries at <http://apps.who.int/globalatlas>. The interactive data query and mapping functions are powerful but take some effort to learn.

A number of commercial organisations offer (for a fee) to help doctors advise travellers. The Australian-based chain of Travel Doctor/Travellers' Medical and Vaccination Centre clinics provides fee-based destination-specific database programs for healthcare providers at <www.traveldoctor.com.au>. Tropimed <www.tropimed.com>, European based, available in different languages, offers a software application (regularly updated for subscribers via CD and a closed internet site) with information on travel medicine aimed at health professionals (doctors, general practitioners and company doctors, pharmacists, medical clinics and hospitals). It is used by the International Committee of the Red Cross. Shoreland Inc <www.shoreland.com>, a US-based commercial travel health information provider, produces an application called Travax EnCompass <www.tripprep.com/scripts/main/default.asp> which is largely based on WHO, CDC and US State Department recommendations. Individual travellers can also gain access via a free online registration. A UK-based commercial provider, MASTA (Medical Advisory Services for Travel Abroad), offers its services via <www.masta-travel-health.com>.

9.2 Resources offering more up-to-date information on changing risks

Weekly Epidemiological Record. This is the official weekly WHO publication that updates the global situation for outbreaks of infectious diseases covered under the International Health Regulations, as well as other diseases of public health importance, including emerging infections. It is released in English and French every Friday and can be downloaded free of charge from <www.who.int/wer/en>. (A subscription to the printed version is also available via: World Health Organization, WHO Press, 20 Avenue Appia, CH-1211 Geneva 27; Fax: +4122) 791 48 57, and there is also an email subscription that sends the table of contents and other epidemiological bulletins.)

Communicable Diseases Intelligence is the open-access journal of the Surveillance Branch, Office of Health Protection, in the Australian Government Department of Health and Ageing. This quarterly publication has an overseas briefs section (though its usefulness is somewhat limited by the quarterly publication) and much of local interest. It is available at no cost by writing to CDI,

P.O. Box 650, Fyshwick ACT 2609; fax 02 6269 1212. CDI is also available online – a link to the current issue is found at <www.health.gov.au/internet/main/publishing.nsf/content/cda-pubs-cdi-cdicur.htm>.

Surveillance and outbreak information

A number of authoritative websites provide routine disease surveillance and outbreak information.

ProMED-mail (the Program for Monitoring Emerging Diseases) is a program of the International Society for Infectious Diseases. It uses a large number of sources (many based on media reports and thus not necessarily substantiated) to provide very rapid email updates on disease outbreaks, whether human, veterinary or in plants. Subscribe via <www.isid.org/promedmail/subscribe.lasso>, or see the latest headlines and search the archives via <www.promedmail.org>. The daily digest option generates the smallest number of incoming emails.

The WHO Global Alert and Response program maintains a website at <www.who.int/csr/en> with disease outbreak news. The 'voice' of the United States Centers for Disease Control and Prevention is the *Morbidity and Mortality Weekly Report* (*MMWR*). It is the CDC's principal means for publication of public health information and recommendations. Find it at <www.cdc.gov/mmwr>. *Eurosurveillance: Europe's journal on infectious disease epidemiology, prevention and control* is a weekly online, open-access publication by the European Centre for Disease Prevention and Control (ECDC) in Stockholm. It can be found at <www.eurosurveillance.org>, and you can subscribe to an email table of contents via the website. The Canadian government's equivalent is the *Canada Communicable Disease Report*, found at <http://origin.phac-aspc.gc.ca/publicat/ccdr-rmtc>. The UK version is the *Health Protection Report* (which superseded the UK *Communicable Disease Report Weekly* in 2007), and a link to the current issue is found at <www.hpa.org.uk/CDR>.

The UK government, together with a number of clinical and academic centres, created the National Travel Health Network and Centre (NaTHNaC) 'to promote clinical standards in travel medicine'. NaTHNaC's website includes a section for health professionals <www.nathnac.org/pro/index.htm> with clinical updates, country-specific information, outbreak surveillance and more. There is also a section for the travelling public (see below).

American physician Dr David Goldberg maintains a website called *MDtravelhealth.com* <www.mdtravelhealth.com> with advice for travel doctors and travellers (which he says is updated daily).

Medical journals

A number of medical journals frequently feature articles on travel medicine. Many provide free access to the table of contents and abstracts, but only some

provide free access to the full articles (and sometimes only some time after the initial publication).

Travel Medicine and Infectious Disease: <www.elsevier.com/wps/find/journaldescription.cws_home/643125/description#description>

Journal of Travel Medicine: <www.wiley.com/bw/journal.asp?ref=1195-1982>

Clinical Infectious Diseases: <http://cid.oxfordjournals.org/content/current>

American Journal of Tropical Medicine and Hygiene: <www.ajtmh.org>

Transactions of the Royal Society of Tropical Medicine and Hygiene: <www.rstmh.org/journals>

Emerging Infectious Diseases Journal: <www.cdc.gov/ncidod/eid/index.htm>

Bulletin of the World Health Organization: <www.who.int/bulletin>

Annals of Tropical Medicine and Parasitology: <www.ingentaconnect.com/content/0003-4983>

Tropical Medicine & International Health: <www.wiley.com/bw/journal.asp?ref=1360-2276>

9.3 Resources for travellers themselves

Travelling Well (2010). Mills DJ. 16th edition. Deborah Mills: Brisbane. ISBN 978-0-9577179-8-5. This practical and very accessible slim book by the founder of the Travel Doctor Clinic in Brisbane is ideal for travellers to take with them. It is updated every 1–2 years. The book is preferred by the majority of Australian Red Cross delegates for this purpose. It can also be downloaded (for $A10) as a PDF file at <www.travellingwell.com.au>, or as an iPhone app (as the 'Travel Health Guide' by WaKi Apps) via the iTunes app store at <http://itunes.apple.com/au/app/travel-health-english/id355832434?mt=8>.

Travellers' Health (2002). Dawood R (ed.). 4th edition. Oxford University Press: Oxford. ISBN 9780192629470. Although getting a bit old now, this is a useful and authoritative, UK-oriented, good reference for intelligent travellers seeking a comprehensive resource. Updates and further information are available from the website of the author's London travel clinic at <www.travellers-health.info>.

Lonely Planet 'Healthy Travel' series (2008). Young I, Gherardin T. 2nd edition, Lonely Planet: Melbourne. There are separate volumes for Africa (ISBN: 9781740591430); Asia and India (ISBN: 9781740591447); Australia, New Zealand and the Pacific (ISBN: 1 86450 052 2 – 1st edition only); and Central and South America (ISBN: 9781740591461). These are generally informative and accessible, compact and inexpensive. We are concerned, however, that the

series presents homeopathic 'vaccinations' as a serious alternative, despite the complete absence of evidence of effectiveness. This could lead the uncritical traveller to miss important vaccinations.

The US Centers for Disease Control and Prevention (CDC) maintains a website with advice for travellers at <wwwnc.cdc.gov/travel>. The UK Foreign and Commonwealth Office offers travellers country-specific advice at <www.fco.gov.uk/en/travel-and-living-abroad>. The Public Health Agency of Canada provides information for the travelling public at <www.phac-aspc.gc.ca/tmp-pmv/info/index-eng.php>.

The UK government's National Travel Health Network and Centre (NaTHNaC) maintains a website for the travelling public at <www.nathnac.org/travel/index.htm> with health risks in destination countries, information sheets with general advice, and reports of disease outbreaks.

A number of websites list travel clinic locations for pre-travel consultations or for travellers to seek 'Western' health care while travelling. The International Society of Travel Medicine maintains a list of travel clinic locations at <www.istm.org/WebForms/SearchClinics/Default.aspx?SearchType=Advanced> (or via its home page at <www.istm.org>). The American Society of Tropical Medicine and Hygiene offers a searchable list of travel medicine consultants at <www.astmh.org/source/ClinicalDirectory>. The non-profit Canadian-based International Association for Medical Assistance for Travellers (IAMAT) has a directory of English-speaking clinicians at <www.iamat.org/doctors_clinics.cfm> as well as other travel health information mostly from WHO and CDC sources at <www.iamat.org>.

The Travel Doctor/TMVC Australia website offers a trip planner for individual travellers at <www.traveldoctor.com.au> as well as an 'ask the travel doctor' feature at <www.traveldoctor.com.au/asktd.html>.

The CIWEC Clinic Travel Medicine Centre maintains a web presence at <www.ciwec-clinic.com>, with information on altitude sickness, travellers' diarrhoea and malaria prevention, with special reference to Nepal, where the clinic is based. The clinic itself was established as a high quality clinic to treat foreign tourists, diplomats and aid workers in Nepal.

A number of governments (including Australia's) provide consular information and/or travel warnings. The Australian Department of Foreign Affairs and Trade site at <www.smartraveller.gov.au> includes an online process for Australian citizens to register their itineraries (to increase their access to local consular support), as well as lists of Australian consulates abroad, travel health advice, and country-specific travel advice and warnings. Each country is given a current rating based on recent events, from 'Be alert to own security' through to 'Do not travel'. The US equivalent is found at <http://travel.state.gov>, the

UK version at <www.fco.gov.uk/travel>, and the Canadian at <www.voyage.gc.ca/index-eng.asp>.

Lonely Planet Publications' website provides health information, among other information for travellers, and many travellers visit the site. The 'travel checklist' is at <www.lonelyplanet.com/bookings/travelChecklistHealth.do>.

9.4 Miscellaneous resources

Medical director

The practice management software package, Medical Director, which is widely used in general practice and updated quarterly, includes a section of travel health. However, this tool provides relatively limited information on country-based risks.

Appendix 1

Common Travel Destinations

This advice is intended as a guide only and may not apply to individual patients or itineraries. Travel health advice should be individualised for a particular patient for a particular trip at a particular time.

The following vaccines are indicated for all these destinations:

- Hepatitis A and typhoid are strongly recommended.
- Travellers should be up-to-date with tetanus, diphtheria, pertussis and polio.

Special vaccines and malarial advice

Destination	Special vaccination	Malaria risk/recommendation	Other issues
Africa – East and West	Meningococcal Yellow fever	MEFLOQUINE, DOXYCYCLINE or MALARONE is generally recommended, although there is little risk in Nairobi and Highlands above 2500 m	Schistosomiasis prevalent in fresh water Rabies prevalent Myiasis (see p. xx) African sleeping sickness
China	JE for long stayers	No malaria prophylaxis is needed for tourists to the usual places. MEFLOQUINE, DOXYCYCLINE or MALARONE is required for Yunnan and Heinan.	Schistosomiasis endemic in central Yangtze River basin
Egypt		Negligible risk. No chemoprophylaxis is necessary.	Schistosomiasis prevalent in fresh water Hepatitis E is endemic
India	Consider meningococcal vaccine if travelling for >2 weeks in northern India, especially around New Delhi. JE vaccine for long-term travellers	MEFLOQUINE, DOXYCYCLINE or MALARONE. Risk areas include the cities of Delhi and Mumbai, as well as in rural areas and areas at altitudes <2000 m (6561 ft)	Rabies is endemic HIV has emerged as a major health issue Dengue and Chikungunya outbreaks have occurred

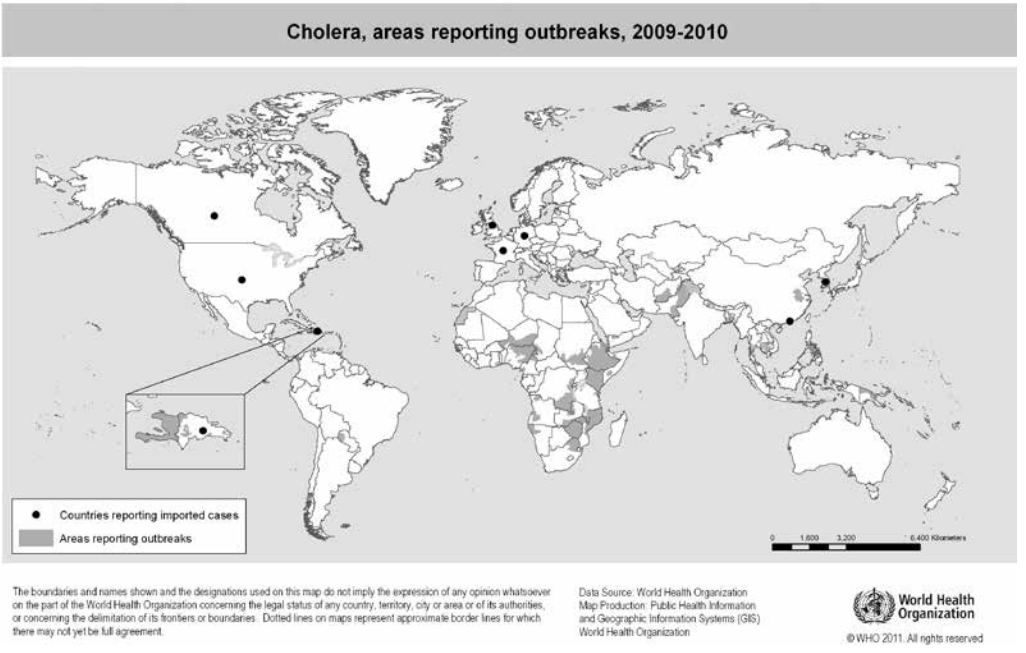
Destination	Special vaccination	Malaria risk/recommendation	Other issues
Indonesia	JE vaccine for long-term travellers	Risk is negligible in Bali. NO malarial prophylaxis is necessary. Risk exists in Lombok and surrounding islands. MEFLOQUINE, MALARONE or DOXYCYCLINE is required for travel to Lombok.	Rabies occurs throughout Indonesia (including Bali) Dengue
Nepal	Japanese encephalitis is endemic in lowlands near the Indian border, e.g. Chitwan National Park and Terai region. Consider vaccination for travel during July to December, especially mid-August to early November. Consider meningococcal vaccine	NO malarial risk if going *only* to Kathmandu/trekking in the Himalayas BUT MEFLOQUINE, DOXYCYCLINE, or MALARONE recommended for those heading south to lowlands near the Indian border (e.g. Chitwan National Park)	High risk for travellers' diarrhoea including Cyclospora infection. Hepatitis E is endemic Altitude sickness for trekkers
Papua New Guinea	Japanese encephalitis for long-term travellers	MEFLOQUINE, DOXYCYCLINE, or MALARONE is recommended for all areas except travel to highland areas only (>1800 m altitude). High intensity of both *P falciparum* and *P vivax* malaria.	High risk of typhoid Rabies does not occur
Solomon Islands		Risk all year round throughout the islands including Honiara. Peak season January to March. MEFLOQUINE, MALARONE or DOXYCYCLINE recommended.	No facilities in Solomon Islands for decompression sickness
South America	Yellow fever vaccination not required for coastal Brazil or coastal Peru	No malaria prophylaxis needed if going to usual tourist areas (e.g Quito, Lima, Cuzco, Machu Picchu, Lake Titicaca, La Paz).	Altitude sickness in some areas. Other infections include Chagas disease (American trypanosomiasis), Schistosomiasis, and cutaneous leishmaniasis.
Thailand	Consider Japanese encephalitis for long-term travellers	NO prophylaxis is usually required for travellers going to Bangkok, central Thailand, Chiang Mai (city) or the major southern coastal resorts (Phuket, Pattaya, Koh Samui, Koh Pee Pee, Koh Samet) BUT DOXYCYCLINE or MALARONE is recommended for those travelling to hilly forested border regions (with Myanmar in the north/west; or Cambodia in the east, where mefloquine resistance has been reported), or spending time in rural parts of peninsular Thailand.	Advice on STI/AIDS essential; regard all sexual contacts as high risk for HIV Rabies is endemic Dengue fever prevalent

Destination	Special vaccination	Malaria risk/recommendation	Other issues
Vanuatu		Rainy season: November-May Futuna Island malaria free MEFLOQUINE, DOXYCYCLINE or MALARONE recommended. Risk for travellers to Port Vila in resort areas and a few days to Tannah is very low.	
Vietnam	Japanese encephalitis vaccination especially for travel to rural areas and Hanoi during May to October.	Low risk in Hanoi, Ho Chi Minh city and the coastal region in between. MEFLOQUINE, DOXYCYCLINE or MALARONE for rural areas to the west.	Dengue is common Rabies is prevalent

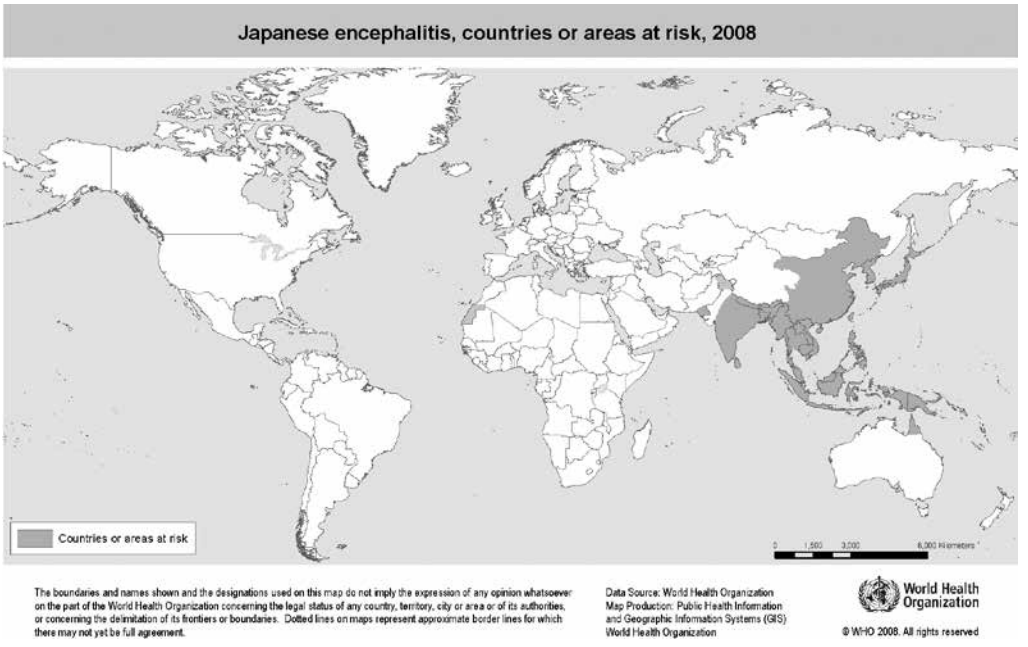
Appendix 2

Infection-distribution Maps

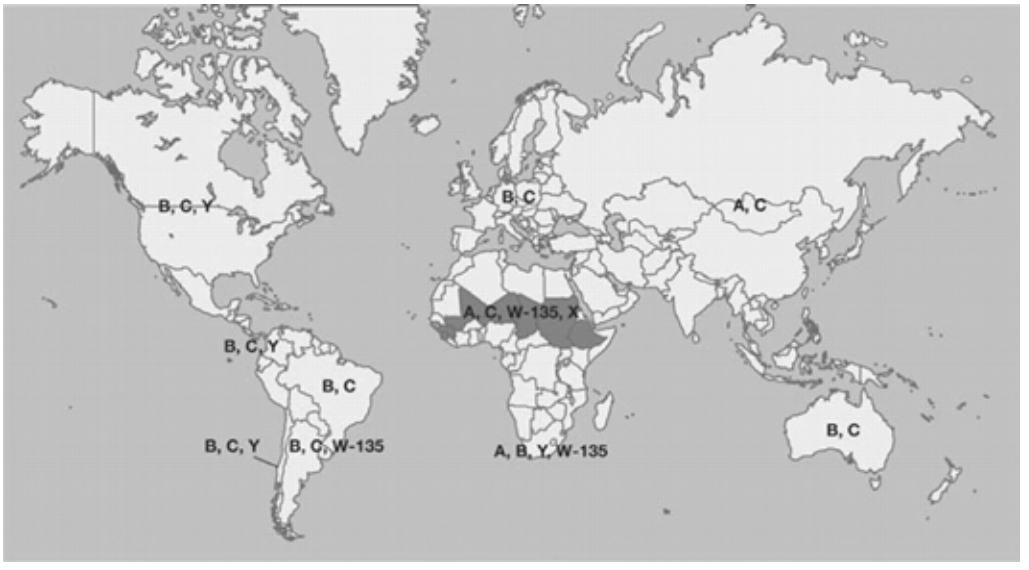
Map 1 Global distribution of cholera



Map 2 Global distribution of Japanese encephalitis

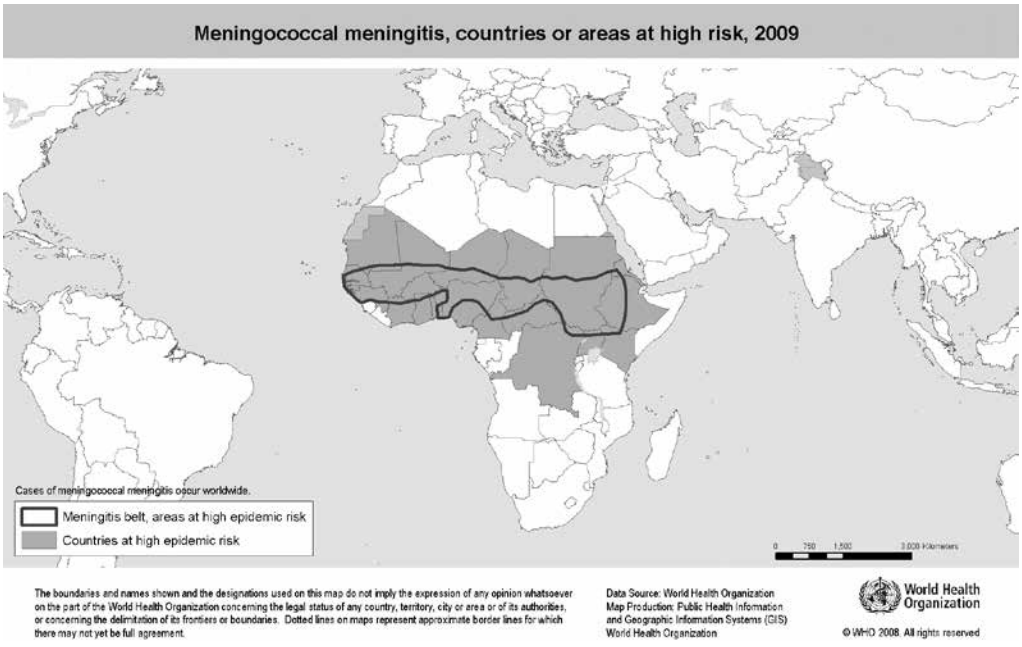


Map 3 Global distribution of predominant meningococcal serogroups



(from Harrison 2009, reproduced with permission)

Map 4 High risk areas for meningococcal meningitis



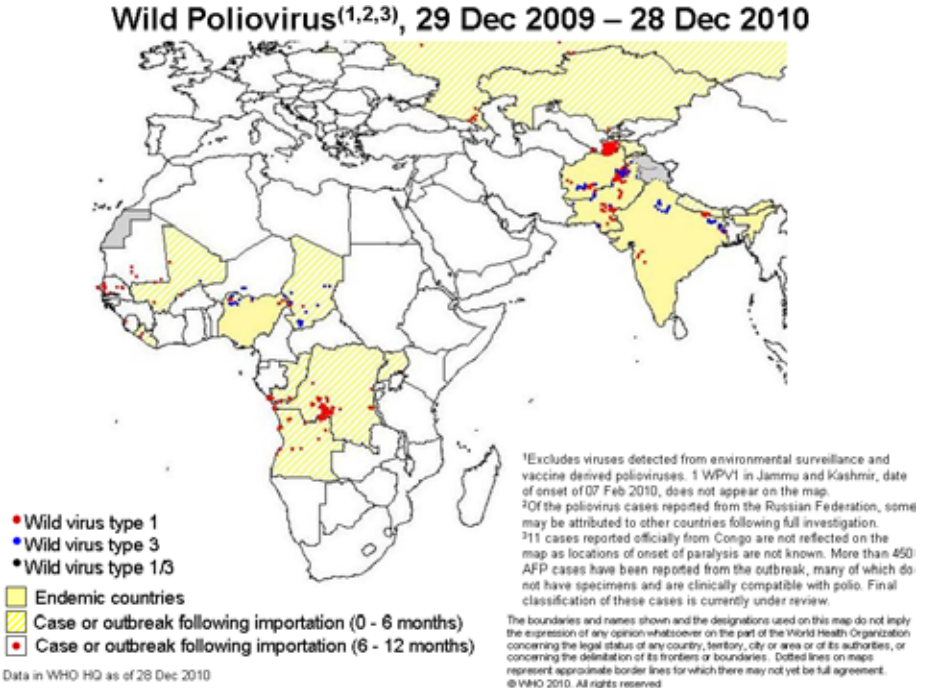
Map 5 Global distribution of hepatitis A

Source: WHO

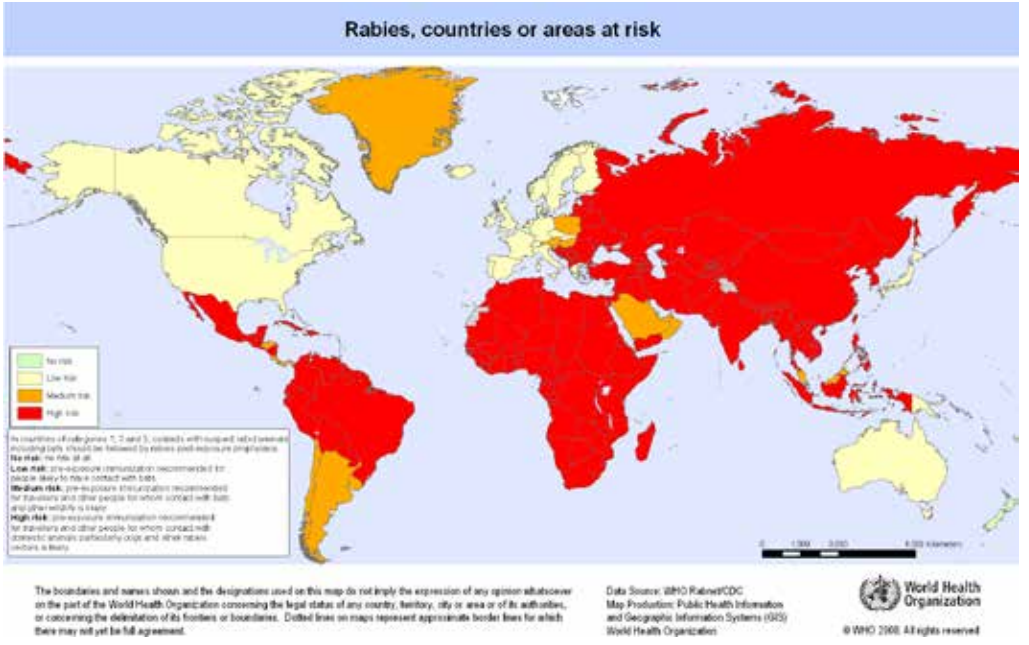
Map 6 Global distribution of hepatitis B

Source: WHO

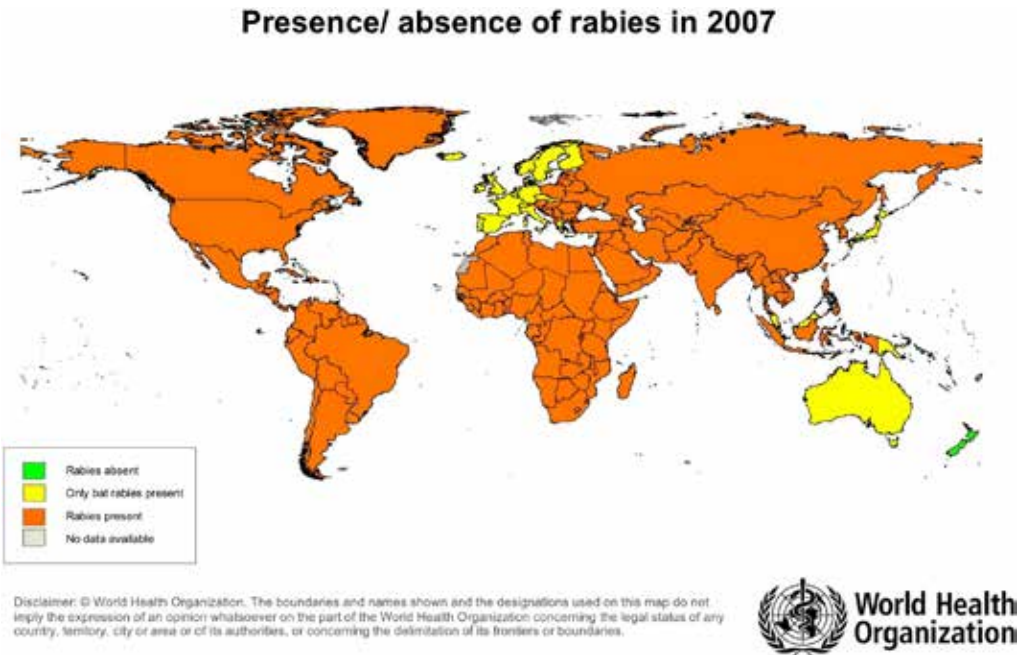
Map 7 Global distribution of poliomyelitis



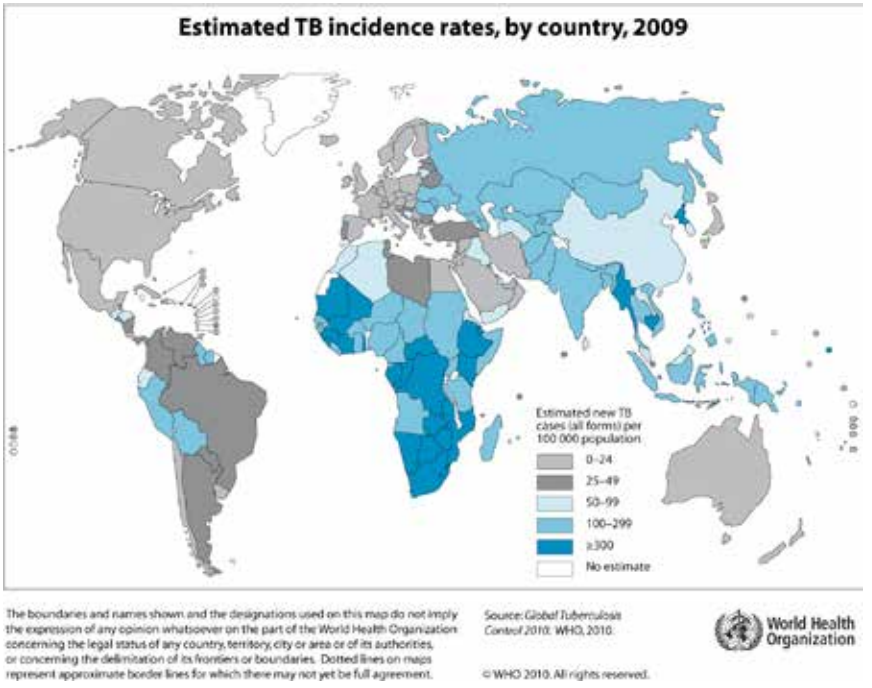
Map 8 Global distribution of rabies



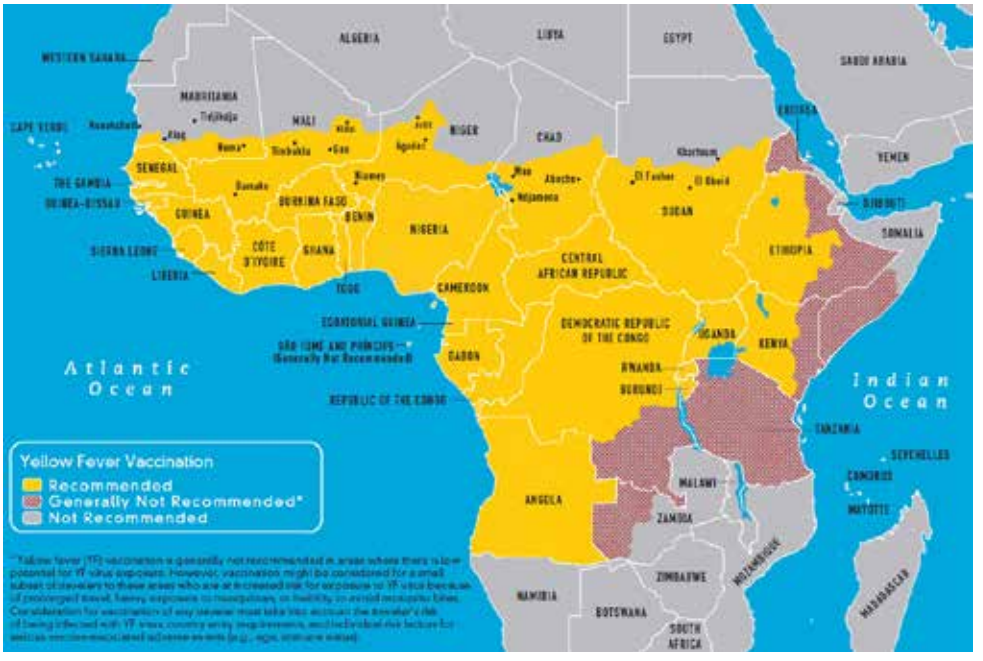
Map 9 Presence/absence of rabies as reported to WHO, 2007



Map 10 Global distribution of tuberculosis



Map 11 Yellow fever vaccine recommendations in Africa

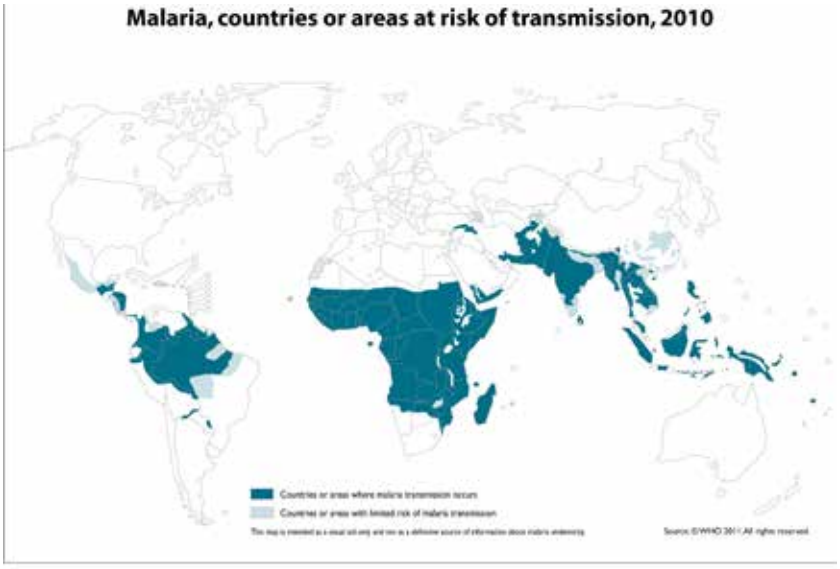


Source: CDC

Map 12 Yellow fever vaccine recommendations in the Americas

Source: CDC

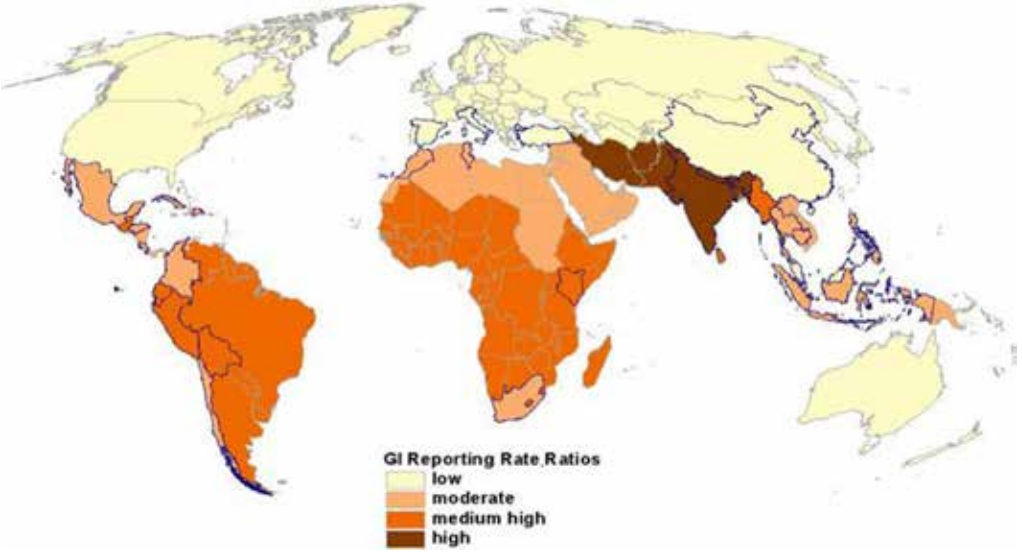
Map 13 Global distribution of malaria



Map 14 Geographic distribution of mefloquine-resistant malaria

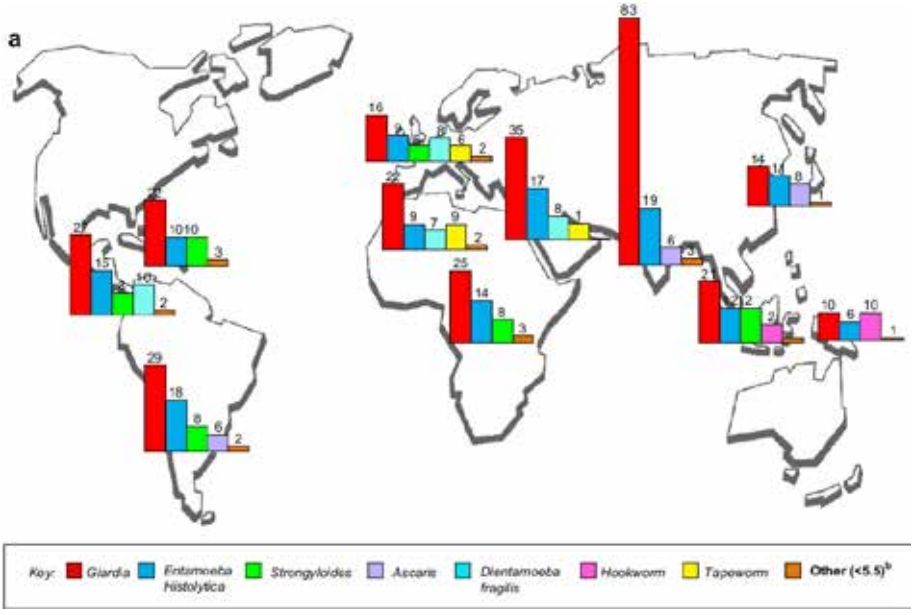
Source: WHO

Map 15 Relative rates of acquisition of gastrointestinal infection by destination



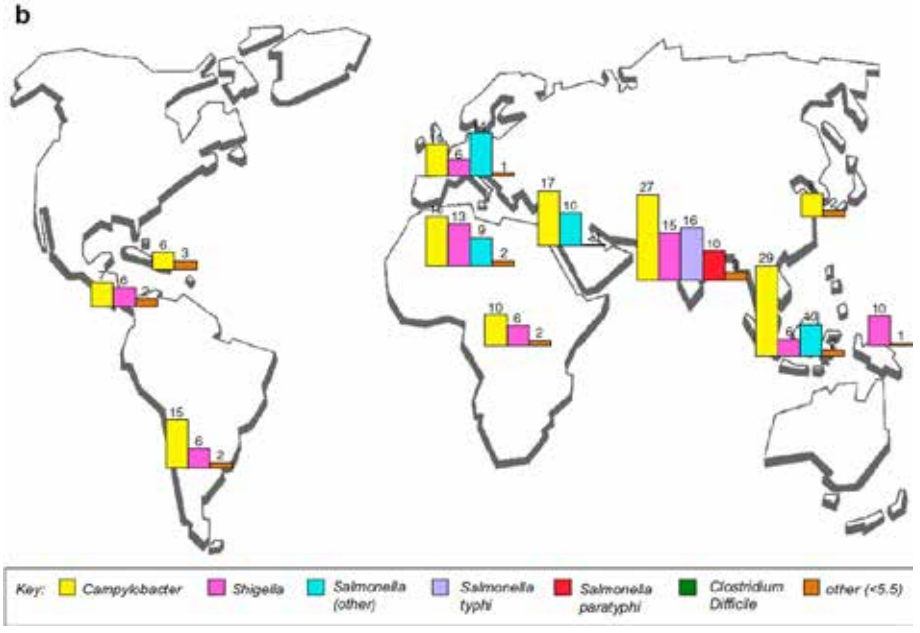
Source: WHO

Map 16 Rates of parasitic pathogens per 1000 returned unwell travellers from a single region



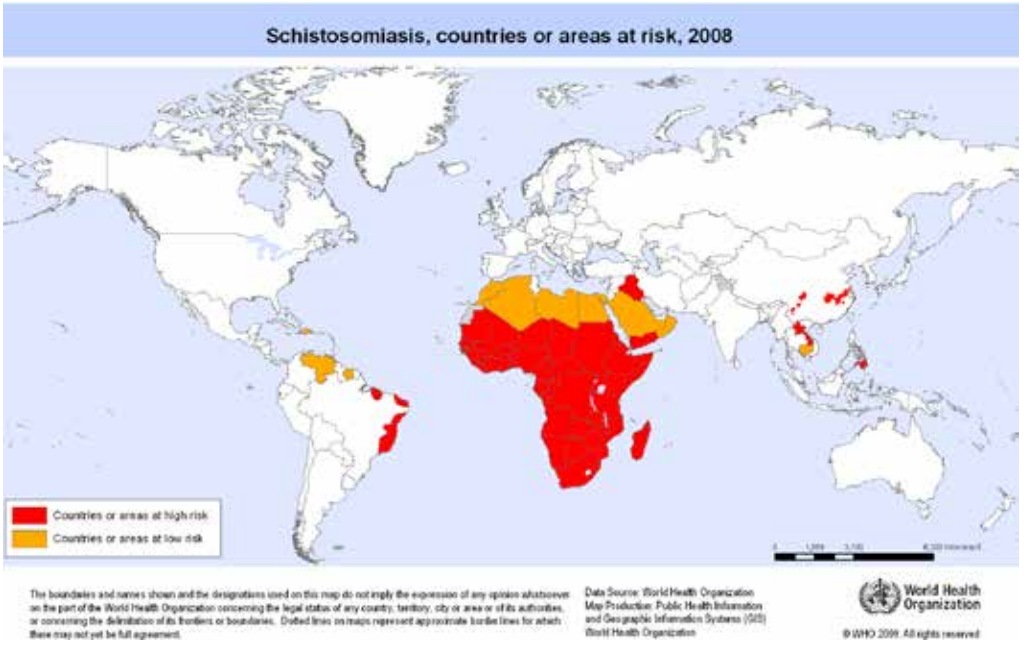
Source: WHO

Map 17 Rates of bacterial pathogens per 1000 returned unwell travellers from a single region

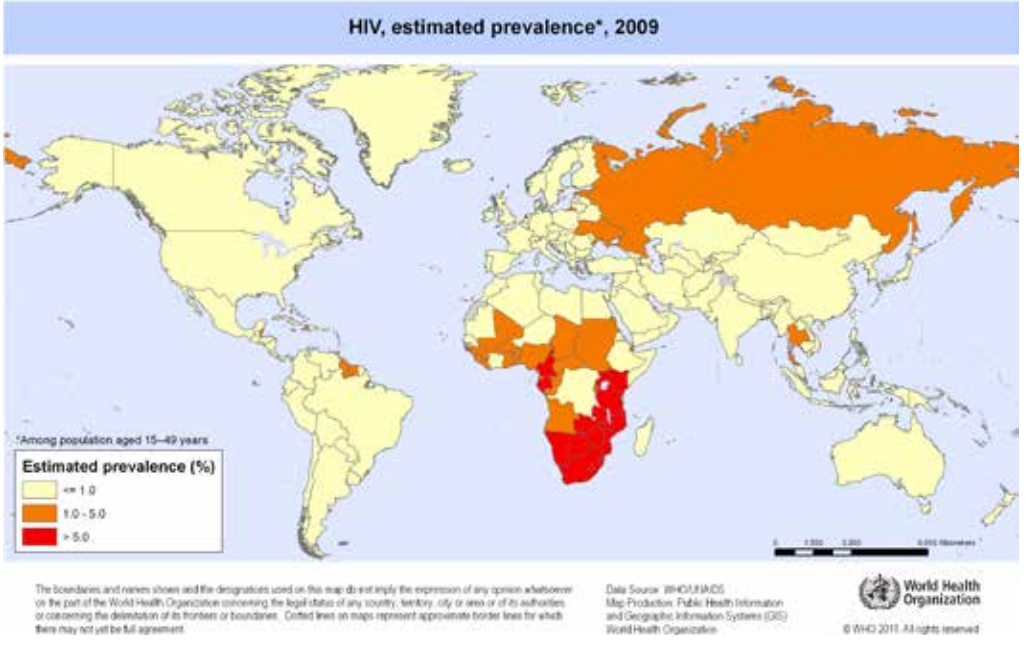


Source: WHO

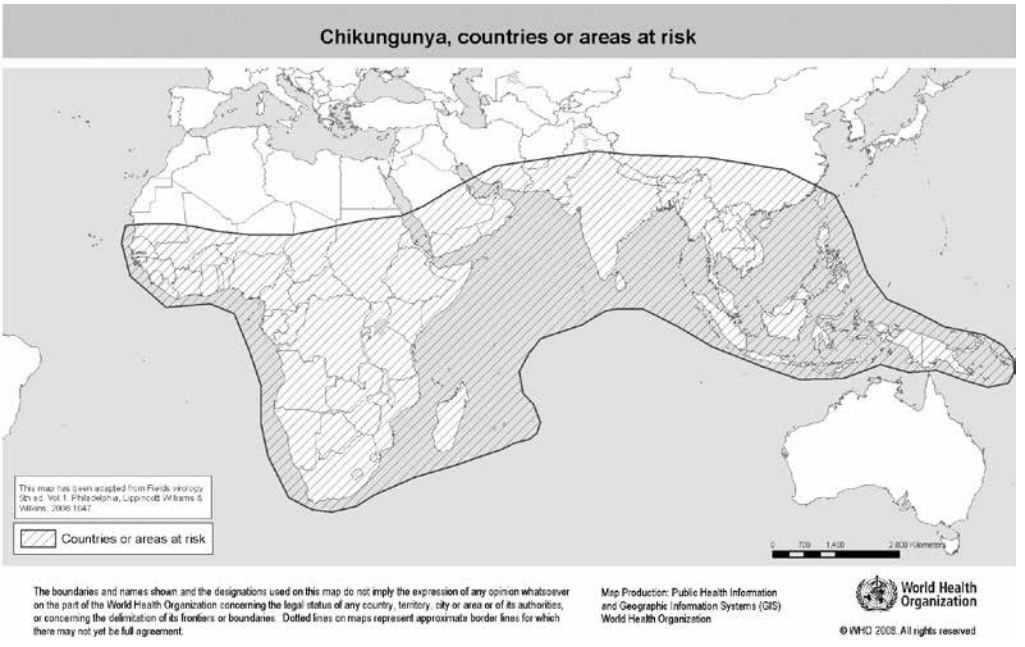
Map 18 Global distribution of schistosomiasis



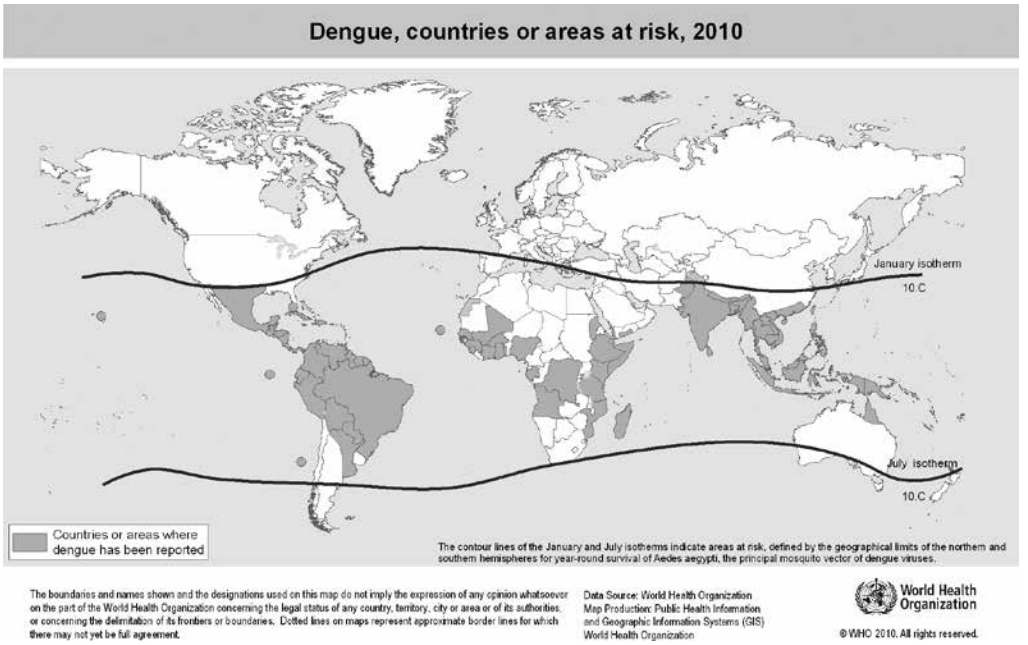
Map 19 Estimated prevalence of HIV in people aged 15–49 years



Map 20 Global distribution of Chikungunya



Map 21 Global distribution of dengue



Appendix 3

Countries: Vaccine Recommendation and Rabies Status

The following recommendations have been adapted from CDC and WHO guidelines. Country requirements for Yellow Fever may change. For current information, we recommend that CDC or WHO websites be checked.

Country	Yellow fever (requirements and recommendations)+	Hep A	Typh	Men	JE	Others	Cholera cases reported in 2008 or 2009#	Rabies free*
Afghanistan	EA	R	R			Polio	Y	
Albania	EA	R	R					
Algeria	EA	R	R					
American Samoa		R	R					Y
Andorra								
Angola	AT, R	R	R			Polio	Y	
Antigua and Barbuda	EA	R						Y
Argentina	S[a]	R	R					
Armenia		R	R			PL, Polio		
Australia	EA[b]				In Torres Strait			Lyssavirus in bats
Austria						TBE, Polio		Y
Azerbaijan		R	R			PL		

Key
JE Japanese encephalitis
PL Plague occurs
TBE Tick-borne encephalitis prevalent
R Vaccination recommended for protection against disease
S Sometimes recommended
Y Yes

\# Countries reporting cholera in 2009 (according to WHO, Weekly Epidemiological Record. 2009; 31(84):309–24 and Weekly Epidemiological Record, 2010; 31(85):293–308). However, cholera vaccine is usually NOT required for travellers, and no country requires proof of cholera vaccination as a condition for entry.

* This includes some countries for which rabies-free status is provisional.

Country	Yellow fever (requirements and recommendations)+	Hep A	Typh	Men	JE	Others	Cholera cases reported in 2008 or 2009#	Rabies free*
Bahamas	EA	S	S					Y
Bahrain	EA	R	R					Y
Bangladesh	EA	R	R		S	Polio		
Barbados	EA	R	R					Y
Belarus		R	R			TBE		
Belgium								Y
Belize	EA	R	R					
Benin	AT, R	R	R	R		Polio	Y	
Bermuda		S	S					Y
Bhutan	EA	R	R	S	S	Polio		
Bolivia	EA, S[c]	R	R			PL		
Bosnia-Herzegovina		R	R					
Botswana	EA	R	R			PL	Y	
Brazil	S[d]	R	R			PL		
Brit. Virgin Islands								Y
Brunei Darussalam	EA	R	R		S			
Bulgaria		S	S					
Burkina Faso	AT, R	R	R	R		Polio		
Burundi	AT, R	R	R			Polio	Y	
Cambodia	EA	R	R		S		Y	
Cameroon	AT, R	R	R	R		Polio	Y	
Canada								
Cape Verde	EA	R	R					Y
Cayman Island		R	S					Y

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Y Yes

Countries reporting cholera in 2009 (according to WHO, Weekly Epidemiological Record. 2009; 31(84):309–24 and Weekly Epidemiological Record, 2010; 31(85):293–308). However, cholera vaccine is usually NOT required for travellers, and no country requires proof of cholera vaccination as a condition for entry.

* This includes some countries for which rabies-free status is provisional.

Country	Yellow fever (requirements and recommendations)+	Hep A	Typh	Men	JE	Others	Cholera cases reported in 2008 or 2009#	Rabies free*
Central African Republic	AT, R	R	R	R		Polio		
Chad	EA, S[e]	R	R	R		Polio	Y	
Chile		R	R					
China	EA	R	R		S	PL	Y	
Christmas Island	EA[b]							Y
Colombia	S[f]	R	R					
Comoros		R	R				Y	
Congo, Republic of the	AT, R	R	R			Polio	Y	
Congo, Democratic Republic of the (formerly Zaire)	AT, R	R	R	R		PL, Polio	Y	
Cook Islands		R	R					Y
Costa Rica	EA	R	R					
Côte d'Ivoire	AT, R	R	R	R		Polio	Y	
Croatia		R	R			TBE		
Cuba		R	R					
Cyprus		R	R					Y
Czech Republic						TBE		Y
Denmark								Y
Djibouti	EA	R	R			Polio	Y	Y
Dominica	EA	R	R					Y
Dominican Rep.		R	R				Y	
East Timor	EA	R	R		S			
Ecuador	EA, S[g]	R	R			PL		
Egypt	EA	R	R					

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\# Countries reporting cholera in 2009 (according to WHO, Weekly Epidemiological Record. 2009; 31(84):309–24 and Weekly Epidemiological Record, 2010; 31(85):293–308). However, cholera vaccine is usually NOT required for travellers, and no country requires proof of cholera vaccination as a condition for entry.

* This includes some countries for which rabies-free status is provisional.

Country	Yellow fever (requirements and recommendations)+	Hep A	Typh	Men	JE	Others	Cholera cases reported in 2008 or 2009#	Rabies free*
El Salvador	EA	R	R					
Equatorial Guinea	EA, R	R	R			Polio		
Eritrea	EA^	R	R	R		Polio	Y	
Estonia						TBE		
Ethiopia	EA, S[h]	R	R	R		Polio	Y	
Falkland Islands								Y
Faroe Island								Y
Fiji	EA	R	R					Y
Finland						TBE		Y
France								Y
French Guiana	AT, R	R	R					
French Polynesia		R	R					Y
Gabon	AT, R	R	R			Polio	Y	
Gambia	EA, R	R	R	R		Polio	Y	
Georgia		R	R			Polio		
Germany						TBE		
Ghana	AT, R	R	R	R		Polio	Y	
Gibraltar								Y
Greece								Y
Greenland								Y
Grenada	EA							
Guadeloupe	EA							Y
Guam		R	R					Y
Guatemala	EA	R	R					

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\# Countries reporting cholera in 2009 (according to WHO, Weekly Epidemiological Record. 2009; 31(84):309–24 and Weekly Epidemiological Record, 2010; 31(85):293–308). However, cholera vaccine is usually NOT required for travellers, and no country requires proof of cholera vaccination as a condition for entry.

* This includes some countries for which rabies-free status is provisional.

Country	Yellow fever (requirements and recommendations)[+]	Hep A	Typh	Men	JE	Others	Cholera cases reported in 2008 or 2009[#]	Rabies free[*]
Guinea	EA, R	R	R	R		Polio	Y	
Guinea-Bissau	AT, R	R	R	R		Polio	Y	
Guyana	EA, R	R	R					
Haiti	EA	R	R				Y	
Honduras	EA	R	R					
Hong Kong		R	R					Y
Hungary						TBE		
Iceland								Y
India	EA	R	R	S	S	PL, Polio	Y	
Indonesia	EA	R	R		S		Y	
Iran	EA	R	R				Y	
Iraq	EA	R	R				Y	
Ireland								Y
Israel		R						
Italy								Y
Jamaica	EA	R	R					Y
Japan					S			Y
Jordan	EA	R	R					
Kazakhstan	EA	R	R			PL, Polio	Y	
Kenya	EA, S[i]	R	R	R		PL, Polio	Y	
Kiribati	EA	R	R					Y
Korea, North	EA	R	R		S			
Korea, South		R	S		S			Y
Kuwait		R	R					Y
Kyrgyzstan		R	R			Polio		
Laos	EA	R	R		S		Y	

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* This includes some countries for which rabies-free status is provisional.

Country	Yellow fever (requirements and recommendations)+	Hep A	Typh	Men	JE	Others	Cholera cases reported in 2008 or 2009#	Rabies free*
Latvia		R				TBE		
Lebanon	EA	R	R					Y
Lesotho	EA	R	R					Y
Liberia	AT, R	R	R	R		Polio	Y	
Libya	EA	R	R					Y
Liechtenstein						TBE		
Lithuania		R	S			TBE		
Luxembourg								Y
Macao		R	S					
Macedonia		R	R					
Madagascar	EA	R	R			PL	Y	
Malawi	EA	R	R				Y	
Malaysia (peninsular)	EA	R	R		S		Y	Y
Malaysia (Sabah)	EA	R	R		S		Y	Y
Malaysia (Sarawak)	EA	R	R		S		Y	Y
Maldives	EA	R	R					Y
Mali	AT, S[e]	R	R	R		Polio	Y	
Malta	EA							Y
Marshall Islands		R	R					Y
Martinique	EA	R	R					Y
Mauritania	EA, S[e]	R	R	S		Polio		
Mauritius	EA	R	R					Y
Mayotte (French)		R	R					

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* This includes some countries for which rabies-free status is provisional.

Country	Yellow fever (requirements and recommendations)[+]	Hep A	Typh	Men	JE	Others	Cholera cases reported in 2008 or 2009[#]	Rabies free[*]
Mexico		R	R					
Moldova		R	R					
Monaco								Y
Mongolia		R	R	S		PL		
Montserrat	EA	S	S					Y
Morocco		R	R					
Mozambique	EA	R	R			PL	Y	
Myanmar	EA	R	R		S	PL	Y	
Namibia	EA	R	R			Polio	Y	
Nauru	EA	R	R					Y
Nepal	EA	R	R	S	S	Polio	Y	
Netherlands								Y
Netherlands Antilles	EA	R	S					Y
New Caledonia	EA	R	R					Y
New Zealand								Y
Nicaragua	EA	R	R					
Niger	AT, S[e]	R	R	R		Polio	Y	
Nigeria	EA, R	R	R	R		Polio	Y	
Niue Island	EA	R	R					Y
Northern Mariana Island		R	R					Y
Norway						TBE		mainland
Oman	EA	R	R					
Pakistan	EA	R	R		S	Polio	Y	
Panama	EA, S[i]	R	R					
Papua New Guinea	EA	R	R		S		Y	Y

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* This includes some countries for which rabies-free status is provisional.

Country	Yellow fever (requirements and recommendations)+	Hep A	Typh	Men	JE	Others	Cholera cases reported in 2008 or 2009#	Rabies free*
Paraguay	EA, R	R	R				Y	
Peru	S[k]	R	R			PL		
Philippines	EA	R	R		S			
Pitcairn	EA							Y
Poland		S	S			TBE		
Portugal		S						Y
Puerto Rico		R	R					
Qatar		R	R					Y
Reunion Island	EA	R	R					Y
Romania		R	R			TBE		
Russian Fed	EA	R	R		S	TBE, Polio		
Rwanda	AT, R	R	R			Polio	Y	
St Helena	EA	R	R					Y
St Kitts	EA	R	R					Y
St Lucia	EA	R	R					Y
St Pierre & Miquelon		R	R					Y
St Vincent	EA	R	R					Y
Samoa (Western)	EA	R	R					Y
San Marino								
São Tomé & Príncipe	AT^	R	R				Y	Y
Saudi Arabia	EA	R	R	R (Hajj and Umrah)				
Senegal	EA, R	R	R	R		Polio	Y	
Serbia/ Montenegro		R	R					

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\# Countries reporting cholera in 2009 (according to WHO, Weekly Epidemiological Record. 2009; 31(84):309–24 and Weekly Epidemiological Record, 2010; 31(85):293–308). However, cholera vaccine is usually NOT required for travellers, and no country requires proof of cholera vaccination as a condition for entry.
* This includes some countries for which rabies-free status is provisional.

Country	Yellow fever (requirements and recommendations)[+]	Hep A	Typh	Men	JE	Others	Cholera cases reported in 2008 or 2009[#]	Rabies free[*]
Seychelles	EA	R	R					Y
Sierra Leone	AT, R	R	R	R		Polio	Y	
Singapore	EA	S	S		S			Y
Slovakia		S	S			TBE		
Slovenia		R	R			TBE		
Solomon Islands	EA	R	R					Y
Somalia	EA[^]	R	R			Polio	Y	
South Africa	EA	R	R				Y	
Spain								except Ceuta/ Melilla
Sri Lanka	EA	R	R		S			
Sudan	EA, S[l]	R	R	R		Polio	Y	
Suriname	EA, R	R	R					
Swaziland	EA	R	R				Y	
Sweden						TBE		Y
Switzerland						TBE		Y
Syria	EA	R	R					
Taiwan		R	R		S			Y
Tajikistan		R	R			Polio		
Tanzania	EA[^]	R	R			PL, Polio	Y	
Thailand	EA	R	R		S		Y	
Togo	AT, R	R	R	R		Polio	Y	
Tonga		R	R					Y
Trinidad & Tobago	EA, S[m]	R	R					
Tunisia	EA	R	R					

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\# Countries reporting cholera in 2009 (according to WHO, Weekly Epidemiological Record. 2009; 31(84):309–24 and Weekly Epidemiological Record, 2010; 31(85):293–308). However, cholera vaccine is usually NOT required for travellers, and no country requires proof of cholera vaccination as a condition for entry.

* This includes some countries for which rabies-free status is provisional.

Country	Yellow fever (requirements and recommendations)+	Hep A	Typh	Men	JE	Others	Cholera cases reported in 2008 or 2009#	Rabies free*
Turkey		R	R					
Turkmenistan		R	R			PL, Polio		
Tuvalu		R	R					Y
Uganda	EA, R	R	R	R		PL, Polio	Y	
Ukraine		R	S					
United Arab Emirates		R	R					Y
United Kingdom								Y
United States						PL		
Uruguay	EA	R	R					Y
Uzbekistan		R	R			Polio		
Vanuatu		R	R					Y
Venezuela	S[n]	R	R					
Vietnam	EA	R	R		S	PL	Y	
Virgin Islands (US)								Y
Yemen Arab Republic	EA	R	R				Y	
Zambia		R	R			Polio	Y	
Zimbabwe	EA	R	R			PL	Y	

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\# Countries reporting cholera in 2009 (according to WHO, Weekly Epidemiological Record. 2009; 31(84):309–24 and Weekly Epidemiological Record, 2010; 31(85):293–308). However, cholera vaccine is usually NOT required for travellers, and no country requires proof of cholera vaccination as a condition for entry.
* This includes some countries for which rabies-free status is provisional.

Yellow fever requirements

AT Countries that require proof of yellow fever vaccination for **all arriving travellers** over 6 months to one year of age (lower age limit varies) (AT = All Travellers). Persons arriving in Australia within 6 days of leaving these countries also require a valid yellow fever certificate.
EA A vaccination certificate is required from travellers coming from areas/countries with risk of yellow fever transmission (EA = from Endemic Areas) (usually only required for individuals over one year of age).
\+ YF vaccine is recommended only for individuals ≥9 months of age.
^ YF vaccine is not usually recommended.

Detailed yellow fever recommendations

a Detailed YF recommendations for Argentina: **Recommended** for all travellers ≥9 months of age who are going to northern and northeastern forested areas of Argentina bordering Brazil and Paraguay <2300 m in elevation. Travellers to designated departments in the following provinces should be vaccinated: Corrientes (Berón de Astrada, Capital, General Alvear, General Paz, Itatí, Ituzaingó, Paso de los Libres, San Cosme, San Martín, San Miguel, Santo Tomé) and Misiones (all departments). Vaccination is also recommended for travellers visiting Iguassu Falls. **Generally not recommended** for travellers whose itinerary is limited to the designated departments in the following provinces <2300 m in elevation: Chaco (Bermejo), Formosa (all departments), Jujuy (Ledesma, San Pedro, Santa Bárbara, Valle Grande), and Salta (Anta, General José de San Martín, Oran, Rivadavia). **Not recommended** for travellers whose itineraries are limited to areas >2300 m in elevation and all provinces and departments not listed above.

b Details of requirements for Australia and Christmas Island: Required for all people ≥1 year of age who enter Australia within 6 days of having stayed overnight or longer in a country with risk of YFV transmission, including São Tomé and Príncipe, Somalia, and Tanzania, but excluding Galápagos Islands in Ecuador and limited to Misiones Province in Argentina.

c Detailed recommendations for Bolivia: **Recommended** for all travellers ≥9 months of age travelling to the following areas east of the Andes Mountains <2300 m in elevation: the entire departments of Beni, Pando, Santa Cruz, and designated areas of Chuquisaca, Cochabamba, La Paz, and Tarija. **Not recommended** for travellers whose itineraries are limited to areas >2300 m in elevation and all areas not listed above, including the cities of La Paz and Sucre.

d Detailed recommendations for Brazil: **Recommended** for all travellers ≥9 months of age going to the following areas: the entire states of Acre, Amapá, Amazones, Distrito Federal (including the capital city of Brasília), Goiás, Maranhão, Mato Grosso, Mato Grosso do Sul, Minas Gerais, Pará, Rondônia, Roraima, Tocantins, and designated areas of the following states: Bahia, Paraná, Piauí, Rio Grande do Sul, Santa Catarina, and São Paulo. Vaccination is also recommended for travellers visiting Iguassu Falls. **Not recommended** for travellers whose itineraries are limited to areas not listed above, including the cities of Fortaleza, Recife, Rio de Janeiro, Salvador, and São Paulo.

e Detailed recommendations for Chad, Mali, Mauritania and Niger: **Recommended** for all travellers ≥9 months of age travelling to areas south of the Sahara Desert. **Not recommended** for travellers whose itineraries are limited to areas in the Sahara Desert.

f Detailed recommendations for Columbia: **Recommended** for all travellers ≥9 months of age travelling to the following departments <2300 m in elevation: Amazonas, Antioquia, Arauca, Atlántico, Bolivar, Boyacá, Caldas, Caquetá, Casanare, Cauca, Cesar, Choco (only the municipalities of Juradó, Riosucio, and Unguía), Córdoba, Cundinamarca, Guainía, Guaviare, Huila, La Guajira (only the municipalities of Albania, and El Molino), Magdalena, Meta, Norte de Santander, Putumayo, Quindio, Risaralda, San Andrés and Providencia, Santander, Sucre, Tolima, Vaupés, and Vichada. **Generally not recommended** for travellers whose itinerary is limited to the following areas west of the Andes <2300 m in elevation: the departments of Cauca, Nariño, Valle de Cauca, and central and southern Choco, and the cities of Barranquilla, Cali, Cartagena, and Medellín. **Not recommended** for travellers whose itineraries are limited to all areas >2300 m in elevation, including the city of Bogotá, and also the municipality of Uribia in the La Guajira department.

g Detailed recommendations for Ecuador: **Recommended** for all travellers ≥9 months of age travelling to the following provinces east of the Andes Mountains <2300 m in elevation: Morona-Santiago, Napo, Orellana, Pastaza, Sucumbios, and Zamora-Chinchipe. **Generally not recommended** for travellers whose itinerary is limited to the following provinces west of the Andes and <2300 m in elevation: Esmeraldas, Guayas, Los Rios, Manabi, and designated areas of Azuay, Bolivar, Canar, Carchi, Chimborazo, Cotopaxi, El Oro, Imbabura, Loja, Pichincha, and Tungurahua. **Not recommended** for travellers whose itineraries are limited to all areas >2300 m in elevation, the cities of Guayaquil and Quito, or the Galápagos Islands.

h Detailed recommendations for Ethiopia: **Recommended** for all travellers ≥9 months of age, except **generally not recommended** for travellers whose itinerary is limited to the Afar and Somali Provinces.

i Detailed recommendations for Kenya: **Recommended** for all travellers ≥9 months of age, except **generally not recommended** for travellers whose itinerary is limited to the following areas: the entire North Eastern Province; the states of Kilifi, Kwale, Lamu, Malindi, and Tanariver in the Coastal Province; and the cities of Mombasa and Nairobi.

j Detailed recommendations for Panama: **Recommended** for all travellers ≥9 months of age travelling to all mainland areas east of the Canal Zone, encompassing the entire comarcas (autonomous territories) of Emberá and Kuna Yala, the entire province of Darién, and areas of the provinces of Colón and Panamá that are east of the Canal Zone. **Not recommended** for travellers whose itineraries are limited to areas west of the Canal Zone, the city of Panama, the Canal Zone itself, the San Blas Islands, and the Balboa Islands.

k Detailed recommendations for Peru: **Recommended** for all travellers ≥9 months of age going to the following areas <2300 m in elevation: the entire regions of Amazonas, Loreto, Madre de Dios, San Martin, and Ucayali and designated areas of the following regions: far northeastern Ancash; northern Apurimac; northern and northeastern Ayacucho; northern and eastern Cajamarca; northwestern, northern, and northeastern Cusco; far northern Huancavelica; northern, central, and eastern Huanuco; northern and eastern Junin; eastern La Libertad; central and eastern Pasco; eastern Piura; and northern Puno. **Generally not recommended** for travellers whose itinerary is limited to the following areas west of the Andes: the entire regions of Lambayeque and Tumbes and the designated areas of west-central Cajamarca and western Piura. **Not recommended** for travellers whose itineraries are limited to the following areas: all areas >2300 m in elevation, areas west of the Andes not listed above, the cities of Cuzco and Lima, Machu Picchu, and the Inca Trail.

l Detailed recommendations for Sudan: **Recommended** for all travellers ≥9 months of age travelling to areas south of the Sahara Desert. **Not recommended** for travellers whose itineraries are limited to areas in the Sahara Desert and the city of Khartoum.

m Detailed recommendations for Trinidad and Tobago: **Recommended** for all travellers ≥9 months of age travelling to the island of Trinidad, except **generally not recommended** for travellers whose itinerary is limited to the urban areas of Port of Spain, cruise ship passengers who do not disembark from the ship, and airplane passengers in transit. **Not recommended** for travellers whose itineraries are limited to the island of Tobago.

n Detailed recommendations for Venezuela: **Recommended** for all travellers ≥9 months of age, except **generally not recommended** for travellers whose itinerary is limited to the following areas: the states of Aragua, Carabobo, Miranda, Vargas, and Yaracuy, and the Distrito Federal. **Not recommended** for travellers whose itineraries are limited to the following areas: the states of Falcón and Lara, the peninsular section of Paez Municipality in Zulia Province, Margarita Island, and the cities of Caracas and Valencia.

Appendix 4

Malaria Risk by Country and Recommendations for Chemoprophylaxis

Adapted from WHO, International Travel and Health; and CDC, Health Information for International Travel.

The authors' recommendations for malaria prophylaxis generally coincide with those of CDC; we differ from WHO principally in recommending doxycycline, mefloquine, or atovaquone–proguanil in situations where WHO recommends chloroquine and proguanil, a combination we do not recommend as a first line option.

Countries and areas not included in this table were free of malaria transmission at time of writing (mid 2011).

Malaria risk by country and recommendations for chemoprophylaxis

Country	Area and/or season	Malaria type	Authors' recommendation
Afghanistan	April to December in all areas below 2000 m	PV + PF CR	2 (if indicated)
Algeria	Malaria risk is limited to one small focus in Sahara region, in Ihrir (Illizi Dept). This area is isolated and access difficult.	PV	None
Angola	Risk exists throughout the year in the whole country	Predominantly PF CR	2
Argentina	Low risk confined to rural areas along borders with Bolivia (lowlands of Jujuy and Salta provinces) and Paraguay (lowlands of Corrientes and Misiones provinces). No transmission at Iguazu falls	PV only	1 (generally none)

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3 doxycycline or atovaquone–proguanil

Country	Area and/or season	Malaria type	Authors' recommendation
Armenia	Focal risk June to October in some villages in Ararat Valley (western border area), mainly in Masis district. No risk in tourist areas	PV only	Generally none
Azerbaijan	Limited risk, May to October in lowland rural areas, mainly between Kura and Arax rivers (provinces of Agcabadi, Barda, Beylaqan, Bilasuvar, Calilabad, Fuzuli, Imisli, Kurdamir, Saatli, Sabirabad and Zardab). No risk in Baku	PV only	Generally none, if indicated 1
Bangladesh	Risk throughout the year in the whole country, excluding Dhaka city	CR widespread along northern and eastern borders with India and Burma and in the south-east	2
Belize	Risk in all districts, highest in southern region. No risk in Belize city or islands most tourists visit	Almost exclusively PV. No resistant PF reported	1 or none
Benin	Risk throughout the year in the whole country	Predominantly PF. CR	2
Bhutan	Risk throughout the year in the southern belt of 5 districts bordering India: Chirang, Samchi, Samdrupjongkhar, Sarpang and Shemgang	CR	2 (if indicated)
Bolivia	Risk throughout the year below 2500 m in departments of Beni, Pando, Santa Cruz and Tarija; and in the provinces of Lacareja, Rurenabaque, and North and South Yungas in La Paz Department. Lower risk exists in Cochabamba and Chuquisaca. No risk in city of La Paz	Predominantly PV. PF in Beni and Pando, especially localities of Guayaramerin, Puerto Rico and Riberalta. CR	2 (if indicated)
Botswana	Risk November to June in northern areas (N of 21°S): Boteti, Chobe, Ngamiland, Okavango, Tutume districts/subdistricts. None in cities of Francistown and Gaborone	Predominantly PF. CR	2
Brazil	Risk in most forested areas below 900 m in the 9 states of the 'Legal Amazonia' region: Acre, Amapa, Amazonas, Maranhao (western part), Mato Grosso (northern part), Para (except Belem City), Rondonia, Roraima and Tocantins. Transmission intensity varies and is higher in jungle areas of mining, logging and agricultural settlements <5 years old than in urban areas. Transmission occurs on the periphery of large cities such as Porto Velho, Boa Vista, Macapa, Manaus, Santarem and Maraba. Risk is negligible or non-existent in states outside 'Legal Amazonia'. No transmission at Iguazu falls.	PV 77%, PF 23%. MDR	2 (if indicated)

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Country	Area and/or season	Malaria type	Authors' recommendation
Burkina Faso	Risk throughout the year in the whole country	Predominantly PF. CR	2
Burundi	Risk throughout the year in the whole country	Predominantly PF. CSR	2
Cambodia	Risk throughout the year in the whole country except in Phnom Penh and close around Lake Tonle Sap. Malaria does occur in the Angkor Wat temple complex.	Predominantly PF. CR MDR – resistance to mefloquine in western provinces near Thai border	2 3 in western provinces
Cameroon	Risk throughout the year in the whole country	Predominantly PF CR	2
Cape Verde	Limited risk September to November in Sao Tiago Island only	CR	2 (generally none)
Central African Republic	Risk throughout the year in the whole country	Predominantly PF CR	2
Chad	Risk throughout the year in the whole country	CR	2
China	Travellers to cities, popular tourist areas, including Yangtze River cruises, and densely populated plains areas are not at risk. Risk, including PF, in Hainan island and Yunnan. Risk of PV in Fujian, Guangdong, Guangxi, Guizhou, Sichuan and Xizang (only along the valley of the Zangbo River in the extreme south-east). Very low risk, but higher in areas of focal outbreaks – PV only – in Anhui, Hubei, Hunan, Jiangsu, Jiangxi and Shandong. Where transmission exists, it occurs only in remote rural communities below 1500 m during warm weather: – north of 33°N – July to Nov – 25°N–33°N – May to Dec – south of 25°N – all year. In general, tourists do not need to take prophylaxis unless they plan to stay in remote rural areas in provinces listed. No risk in Hong Kong or Macau Semi-Autonomous Regions	Predominantly PV. MDR along China–Myanmar border (resistance to mefloquine)	2 in Hainan, most of Yunnan Province. 1 in other areas 3 along China–Myanmar border in western part of Yunnan Province. Many areas, none

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Country	Area and/or season	Malaria type	Authors' recommendation
Colombia	Risk high throughout the year in rural and jungle areas below 800 m, especially in regions of Amazonia, Orinoquia, Pacifico and Uraba-Bajo Cauca. Transmission intensity varies between departments, with highest risk in in Amazonas, Choco, Cordoba, Guainia, Guaviare, Putumayo and Vichada. No risk in Bogota and vicinity.	PF 46%, PV 54%. CRPF in Amazonia, Pacifico and Uraba-Bajo Cauca. CSR	2 (if indicated)
Comoros	Risk throughout the year in the whole country	Predominantly PF. CR	2
Congo (Republic of the)	Risk throughout the year in the whole country	Predominantly PF. CR	2
Congo, Democratic Republic of the (formerly Zaire)	Risk throughout the year in the whole country	Predominantly PF. CR	2
Costa Rica	Moderate risk throughout the year in the cantons of Los Chiles (Alajuela Province), and Matina and Talamanca (Limon Province). Lower risk in provinces of Guanacaste and Heredia, and in other cantons in provinces of Alejuela and Limon. Negligible or low risk in other cantons	Almost exclusively PV	1 (or none)
Côte d'Ivoire	Risk throughout the year in the whole country	Predominantly PF. CR	2
Djibouti	Risk throughout the year in the whole country	Predominantly PF. CR	2
Dominican Republic	Low risk throughout the year, especially in rural areas of western provinces (bordering Haiti), such as Castanuelas, Hondo Valle and Pepillo Salcedo. No risk in cities of Santiago and Santo Domingo.	Exclusively PF. No resistance to any antimalarial drug	1
East Timor	Risk throughout the year in the whole country	Predominantly PF. CR	2
Ecuador	Risk throughout the year below 1500 m. Highest risk in El Oro, Esmeraldas and Manabi. Some risk in Cotopaxi, Loja and Los Rios. No risk in cities of Guayaquil or Quito, the central highland tourist areas, or in the Galápagos Islands	PF 23%, PV 77%. CRPF (especially Esmeraldas Province)	2 (if indicated)

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Egypt	Very limited risk June to October in the El Faiyum governorate only (no cases reported since 1998). No risk in tourist areas including Nile River cruises.	PF + PV	None
El Salvador	Very low risk throughout the year in Santa Ana Province, in rural areas of migratory influence from Guatemala	Almost exclusively PV	1 (or none)
Equatorial Guinea	Risk throughout the year in the whole country	Predominantly PF. CR	2
Eritrea	Risk throughout the year in the whole country below 2200 m. No risk in Asmara	Predominantly PF. CR	2
Ethiopia	Risk throughout the year in the whole country below 2000 m. No risk in Addis Ababa	Predominantly PF. CR	2 (if indicated)
French Guiana	Risk high throughout the year in 9 municipalities bordering Brazil (Oiapoque river valley) and Suriname (Maroni river valley). Risk low or negligible in the other 13 municipalities	PF 70%, PV 30%.	2 (if indicated)
Gabon	Risk throughout the year in the whole country	Predominantly PF. CR	2
Gambia	Risk throughout the year in the whole country	Predominantly PF. CR	2
Georgia	Focal risk July to October in some villages in the south-eastern part of the country	Exclusively PV	1 (if indicated)
Ghana	Risk throughout the year in the whole country	Predominantly PF. CR	2
Guatemala	Risk throughout the year in rural areas below 1500 m. High risk in departments of Alta Verapaz, Baja Verapaz, Peten and San Marcos; and moderate risk in departments of Escuintla, Huehuetenango, Izabal, Quiche, Retalhuleu, Suchitepequez and Zacapa. No risk in Antigua, Lake Atitlan or Guatemala City	Predominantly PV	1 (or none)
Guinea	Risk throughout the year in the whole country	Predominantly PF. CR	2
Guinea-Bissau	Risk throughout the year in the whole country	Predominantly PF. CR	2

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Country	Area and/or season	Malaria type	Authors' recommendation
Guyana	Risk high throughout the year in all parts of the interior; sporadic cases also reported along the coastal belt	PF 48%, PV 52%. CR	2
Haiti	Risk throughout the year in the whole country	Exclusively PF. CS	1
Honduras	Risk throughout the year in 223 municipalities; low in the other 71 municipalities, including San Pedro Sula and city of Tegucigalpa. PF risk highest in Sanitary Region VI, including Roatan and other Bay Islands	Predominantly PV. CS	1
India	Risk throughout the year in the whole country below 2000 m, including the cities of Delhi and Mumbai. No transmission in areas >2000 m in states of Himachal Pradesh, Jammu and Kashmir, and Sikkim (i.e. no risk in mountainous areas of northern states).	PF 40–50%. CR	2
Indonesia	Risk throughout the year in the whole country except in cities of Java and Sumatra, and resort areas of Bali and Java. Risk at east Javanese temple complex of Borobudur. Risk highest in Irian Jaya	CR PF. CRPV reported, especially from Irian Jaya	2 None for travellers only to Bali
Iran	PF risk in March to November in south-east – rural areas of provinces of Hormozgan, Kerman (southern tropical part) and Sistan-Baluchestan. Limited PV risk in some areas north of the Zagros mountains and in western and south-western regions during summer months, in provinces of Fars, Boshehr, Khuzestan, Ilam, Lorestan, Chamahal and Bakhtiari.	CR	2
Iraq	Low risk from May to November in Basrah Province and in areas in the north below 1500 m – Duhok, Erbil, Ninawa, Sulaimaniya and Ta'min provinces. No risk in Baghdad	PV exclusively	Usually none
Jamaica	Rare cases in Kingston	PF	Usually none

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Country	Area and/or season	Malaria type	Authors' recommendation
Kenya	Risk throughout the year in the whole country. Normally little risk in city of Nairobi and in highlands above 2500 m of Central, Eastern, Nyanza, Rift Valley and Western provinces.	CR	2
Korea, Democratic People's Republic of (North)	Limited risk in some southern areas	Exclusively PV	1 (Generally none)
Korea, Republic of (South)	Limited risk mainly in northern areas of Kyunggi Do and Gangwon Do provinces	Exclusively PV	1 (Generally none)
Kyrgyzstan	Risk from June to September in some southern and western areas bordering Tajikistan and Uzbekistan, mainly in Batken, Osh and Zhele-Abadskaya provinces	Exclusively PV	1 (Generally none)
Lao People's Democratic Republic	Risk throughout the year in the whole country except in Vientiane	Predominantly PF. CR MDR-resistance to mefloquine along Laos–Myanmar border and along Laos–Thai border	2 or 3 for areas with mefloquine resistance
Liberia	Risk throughout the year in the whole country	Predominantly PF. CR	2
Madagascar	Risk throughout the year in the whole country, highest in coastal areas	Predominantly PF. CR	2
Malawi	Risk throughout the year in the whole country	Predominantly PF. CR	2
Malaysia	Risk throughout the year only in limited hinterland foci; urban and coastal areas are free of malaria	CR	2 (Generally none)
Mali	Risk throughout the year in the whole country	Predominantly PF. CR	2
Mauritania	Risk throughout the year in the whole country, except in the northern areas: Dakhlet-Nouadhibou and Tiris-Zemour. In Adrar and Inchiri, risk occurs during the rainy season (July to October)	CR	2 (if indicated)
Mauritius	Risk may exist in certain rural areas. No risk on Rodrigues Island	Exclusively PV	1 (generally none)

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Country	Area and/or season	Malaria type	Authors' recommendation
Mayotte	Risk throughout the year	Predominantly PF. CR	2
Mexico	Risk in some rural areas in the south not often visited by tourists. High risk of transmission in some localities in states of Chiapas, Quintana Roo, Sinaloa and Tabasco; moderate risk in states of Chihuahua, Durango, Nayarit, Oaxaca and Sonora; and low risk in Campeche, Guerrero, Michoacan, and Jalisco (mountainous northern areas only). No risk along Mexico–US border, or in major resorts along the Pacific and Gulf coasts.	Almost exclusively PV. CS	1 (generally none)
Morocco	Very limited risk may exist May to October in certain rural areas of Chefchaouen Province. No risk in Tangier, Rabat, Casablanca, Marrakech or Fes.	Exclusively PV. CS	None
Mozambique	Risk throughout the year in the whole country	Predominantly PF. CR	2
Myanmar (formerly Burma)	Risk exists commonly below 1000 m: throughout the year in Karen state March to December in Chin, Kachin, Kayah, Mon, Rakhine and Shan states; Pegu Division; and Hlegu, Hmawbi, and Taikkyi townships of Yangon Division April to December in rural areas of Tenasserim Division May to December in Irrawaddy Division and rural areas of Mandalay Division June to November in rural areas of Magwe Division, and in Sagaing Division No risk in cities of Yangon (Rangoon) or Mandalay	Predominantly PF. CR; mefloquine resistance in eastern part of Shan State. PV with reduced sensitivity to chloroquine reported	3 in eastern Burma (near Thai border in Shan, Kayah and Karen states); elsewhere 2
Namibia	Risk November to June in northern regions – provinces of Kunene, Caprivi, Ohangwena, Okavango, Omaheke, Omusati, Oshana, Oshikoto and Otjozondjupa; and throughout the whole year along the Kavango and Kunene Rivers	Predominantly PF. CR	2
Nepal	Risk throughout the year below 1200 m in rural areas of the Terai and Hill districts of Bara, Dhanuka, Kapilvastu, Mahotari, Parsa, Rautahat, Rupendehi and Sarlahi, especially along the Indian border. No risk in Kathmandu or on typical Himalayan treks	Predominantly PV. CR	2 (if indicated)

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Country	Area and/or season	Malaria type	Authors' recommendation
Nicaragua	Risk throughout the year in rural areas and outskirts of Managua, in 119 municipalities, with highest risk in Chinandega, Jinotega, Nueva Segovia, RAAN, RAAS and Rio San Juan. In the other 26 municipalities, in the departments of Carazo, Madriz and Masaya, transmission is low or negligible	Predominantly PV. CS	1
Niger	Risk throughout the year in the whole country	Predominantly PF. CR	2
Nigeria	Risk throughout the year in the whole country	Predominantly PF. CR	2
Oman	Very limited risk may exist in remote areas of Musandam Province. No cases reported since 2001	CR	None
Pakistan	Risk throughout the year in the whole country below 2000 m, including all cities	CR	2
Panama	Low risk throughout the year in rural areas in 3 provinces: Bocas del Toro in the west, and Darien and San Blas in the east. Elsewhere – including Panama City and former Canal Zone – no or negligible risk.	Predominantly PV. CR reported in Darien and San Blas provinces.	2 if travel includes eastern endemic areas
Papua New Guinea	Risk throughout the year in the whole country below 1800 m	Predominantly PF. CR	2
Paraguay	Moderate risk in certain municipalities of the departments of Alto Parana, Caaguazu and Canendiyu. In the other 14 departments there is no or negligible risk.	Exclusively PV. CS	1 (or none)
Peru	Risk in all departments except Arequipa, Moquegua, Puno and Tacna. Travellers who visit only Lima and its vicinity, coastal areas south of Lima, or the highland tourist areas (Cuzco, Machu Picchu and Lake Titicaca) are not at risk and need no prophylaxis	PF 22%, PV 78%. PF transmission reported in Jaen, Lambayeque, Loreto, Luciano Castillo, Piura, San Martin, Tumbes and Ucayali. CR	2 (or none)
Philippines	Risk throughout the year below 600 m, except in provinces of Aklan, Bilaran, Bohol, Camiguin, Capiz, Catanduanes, Cebu, Guimaras, Iloilo, Leyte, Masbate, northern Samar, Sequijor and metropolitan Manila. No risk in urban areas or in the plains	CR	2 (or none)

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Country	Area and/or season	Malaria type	Authors' recommendation
Rwanda	Risk throughout the year in the whole country	Predominantly PF. CR	2
São Tomé and Príncipe	Risk throughout the year	Predominantly PF. CR	2
Saudi Arabia	Risk throughout the year in most of the Southern Region (except in the high altitude areas of Asir Province) and in certain rural areas of the Western region. Provinces with risk are Jizan, and rural areas of Al Madinah, Makkah, Ramya, Bishah, Asir, Najran and Al Bahah. No risk in Jeddah, Mecca, Medina and Taif cities, and Eastern, Northern and Central Provinces	Predominantly PF. CR	2 (if indicated)
Senegal	Risk throughout the year in the whole country. Less risk January–June in central western regions.	Predominantly PF. CR	2
Sierra Leone	Risk throughout the year in the whole country	Predominantly PF. CR	2
Solomon Islands	Risk throughout the year in the whole country, except for the southern province of Rennell and Bellona, the eastern province of Temotu, and the outer islands of Tikopia, Anuta and Fatutaka	Predominantly PF. CR	2
Somalia	Risk throughout the year in the whole country	Predominantly PF. CR	2
South Africa	Risk throughout the year in low altitude areas of Mpumalanga Province (including Kruger National Park), Northern Province and north-eastern KwaZulu-Natal as far south as the Tugela River. Risk is highest October to May	Predominantly PF. CR	2 (or none)
Sri Lanka	Risk exists throughout the year, except in the districts of Colombo, Galle, Kalutara and Nuwara Eliya	PF 13%, PV 87%. CR	2 (if indicated)
Sudan	Risk throughout the year in the whole country. Risk is low and seasonal in the north; higher along the Nile south of Lake Nasser and in the central and southern part of the country. Risk on the Red Sea coast is very limited	Predominantly PF. CR	2
Suriname	Risk is high throughout the year in the 3 southern districts. In Paramaribo city and the 7 other coastal districts (Nickerie, Coronie, Saramacca, Wanica, Commewijne and Marowijne), risk is low or negligible	PF 76%. CR. Some decline in quinine sensitivity reported.	2

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Country	Area and/or season	Malaria type	Authors' recommendation
Swaziland	Risk throughout the year in all low veld areas (mainly Big Bend, Mhlume, Simunye and Tshaneni)	Predominantly PF. CR	2 (or none)
Syrian Arab Republic	Limited risk May to October in foci along the northern border, especially in the north-eastern part of the country (El Hassaka province)	Exclusively PV. CS	1 (usually none)
Tajikistan	Risk from June to October, particularly in southern border areas (Khatlon region), and in some central (Dushanbe), western (Gorno-Badakhshan), and northern (Leninabad region) areas	Predominantly PV. CR PF reported in southern part of the country	2 (if indicated)
Tanzania, United Republic of	Risk throughout the year in the whole country below 1800 m	Predominantly PF. CR	2 (if indicated)
Thailand	Risk throughout the year in rural, especially forested and hilly, areas of the whole country, mainly towards international borders. No risk in cities, main resort areas, and southern coastal areas (including Bangkok, Chiangmai, Chiangrai, Pattaya, Phuket and Koh Samui). For most tourists the risk is low and prophylaxis not justified	CSR; MDR: resistance to mefloquine and quinine reported near the border with Cambodia and along northern part of border with Myanmar	2; 3 in areas bordering Cambodia and Myanmar (Burma) Often none
Togo	Risk throughout the year in the whole country	Predominantly PF. CR	2
Turkey	Risk from May to October mainly in the south-eastern part of the country, and in Amikova and Cukurova plain. Provinces with risk are Adana, Adiyaman, Batman, Bingol, Bitlis, Diyarbakar, Elazig, Gaziantep, Hakkari, Hatay, Icel, Kahramanmaras, Kilis, Mardin, Mus, Osmaniye, Sanliurfa, Siirt, Sirnak and Van. No risk in the main tourist areas in the west and south-west of the country, or on typical cruises.	Exclusively PV. CS	1 (or none)
Turkmenistan	Risk June to October in some south-eastern villages, mainly in Mary district	Exclusively PV. CS	1 (generally none)
Uganda	Risk throughout the year in the whole country, including the main towns of Fort Portal, Jinja, Kampala, Mbale and parts of Kigezi	Predominantly PF. CR	2
Uzbekistan	Sporadic cases are reported from Surkhandarinskaya Region (Uzunskiy, Sariassiskiy and Shuchinskiy districts)	Exclusively PV. CS	1 (generally none)

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Vanuatu	Low to moderate risk throughout the year in the whole country	Predominantly PF. CSR; PV resistant to chloroquine reported	2
Venezuela	Risk in rural areas: – PV in some rural areas of Apure, Amazonas, Barinas, Bolivar, Sucre and Tachira states PF restricted to municipalities in jungle areas of Amazonas (Atabapo), Bolivar (Cedeno, Gran Sabana, Raul Leoni, Sifontes and Sucre) and Delta Amacuro (Antonia Diaz, Cascoima and Pedernales). Risk in Angel Falls. No risk in Caracas, towns, central and western coastal areas	CRPF in interior of Amazonas state	2 (if indicated)
Vietnam	Risk mainly in rural areas. No risk in urban centres (including Hanoi, Ho Chi Minh City, Da Nang, Nha Trang, Qui Nhon and Haiphong), the Red River delta, and the coastal plain areas of central Vietnam north of Nha Trang High risk areas are the highlands below 1500 m south of 18°N, notably the 3 central highland provinces of Dak Lak, Gia Lai and Kon Tum, as well as the southern provinces of Ca Mau, Bac Lieu and Tay Ninh. Rare cases in Mekong Delta	Predominantly PF. CR	2 (or none)
Yemen	Risk throughout the year, but mainly September to February, in the whole country below 2000 m. No risk in Sana'a city	Predominantly PF. CR	2 (if indicated)
Zambia	Risk throughout the year in the whole country	Predominantly PF. CR	2
Zimbabwe	Risk all year in Zambezi valley, and November to June in rest of the country below 1200 m. In Harare and Bulawayo, risk is negligible	Predominantly PF. CR	2 (if indicated)

Countries with only *P vivax* risk
Algeria, Argentina, Armenia, Azerbaija, Georgia, Iraq, Korea – DPRK (North) and ROK (South), Mauritius, Morocco, Syria, Turkey, and Turkmenistan

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Appendix 5

Vaccines: Route, Schedule, Lower Age Limit, Accelerated Regimens

Vaccine	Route	Primary course	Booster	Usual lower age limit	Accelerated regimen
Cholera (Dukoral)	oral	2 doses 0, 1–6 weeks	3 years for adults; 6 months children <5 years	2 years	–
Haemophilus influenzae	IM	HbOC, PRP-T 2, 4, 6 months PRP-OMP 2, 4 months	12 months 12 months	6 weeks 6 weeks	minimum interval of 4 weeks between doses
Hepatitis A (Havrix)	IM	Adults: single dose 1440 EIA U Children 1–15: 720 EIA U	1440 EIA U at 6–12 months Children 1–15: 720 EIA U at 6–12 months	1 year	–
Hepatitis A (Vaqta)	IM	Adults: single dose 50 U Children 1–17: 25 U	50 U at 6–18 months Children 2–17: 25 U at 6–18 m	1 year	–
Hepatitis A/Typhoid fever Vivaxim	IM	1 mL 0.025 mg Sal typhi Vi polysaccharide (Ty2 strain) Hepatitis A antigen 160 EIA U	6 months for hepatitis A 3 years for typhoid fever	2 years	–
Hepatitis B	deep IM	0, 1, 6 months	see text	none	0,1, 2, 6 months
Hepatitis A & B Twinrix	IM	Adults: Twinrix (720/20) Children: Twinrix junior (1–15 years) (360/10) 0, 1, 6 months	none	1 year	0, 7, 21 days, 12 months
Influenza	SC	Adults: single dose Children & adults with impaired immune function: 2 doses 4 weeks apart	yearly	6 months	–
Japanese B encephalitis: JESPECT	IM	2 × 0.5 mL doses on day 0, 28	2 years for most travellers (12 months if high risk destination)	Not approved under 17 years of age	–

Vaccine	Route	Primary course	Booster	Usual lower age limit	Accelerated regimen
Japanese B encephalitis: IMOJEV	SC	Single 0.5 mL dose	Unclear (likely to provide adequate protection for 5 years or more)	12 months	–
Measles/Mumps/Rubella – MMR	IM or SC	12 months	4 years	12 months (see text)	9 months of age, repeated at 12 months
Meningococcal, polysaccharide vaccine	deep SC	1 dose	3 years	2 years (see text)	–
Meningococcal C conjugate vaccine	IM	Infants, 2, 4, 6 months Infants aged 4–11 months; 2 doses at least 4 weeks apart Children 12 months and over; single dose	none	6 weeks	–
Quadrivalent meningococcal vaccine (Menactra)	IM	Single 0.5 mL dose	Unknown	2 years (see text)	–
Quadrivalent meningococcal vaccine (Menveo)	IM	Single 0.5 mL dose	Unknown	11 years (see text)	–
Plague	deep SC	Adults: 2 doses 1–4 weeks apart Children <12 years: 3 doses 1–4 weeks apart	6 months 6 months	6 months	–
Pneumococcal polysaccharide	deep SC or IM	1 dose	5 years	2 years	–
Pneumococcal conjugate (13vPCV)	IM	3 doses 2, 4, 6 months	none	6 weeks	minimum interval of 4 weeks between doses
Poliomyelitis (OPV)	oral	3 doses 2, 4, 6 months	10 years	6 weeks	minimum interval of 4 weeks between doses
Poliomyelitis (eIPV)	deep SC	3 doses 2, 4, 6 months; 4th dose at 4 years of age for infants	10 years	none	minimum interval of 4 weeks between doses

Vaccine	Route	Primary course	Booster	Usual lower age limit	Accelerated regimen
Rabies	IM or deep SC	3 doses on day 0, 7 28	1 dose every 3 years (see text)	none	–
Tetanus/ Diphtheria (dTPa/dTpa)	IM	3 doses 2 months apart	4 years and thereafter 10-yearly	6 weeks	minimum intervals between 1st and 2nd, and 2nd and 3rd doses: 4 weeks minimum interval between 3rd and 4th dose: 6 months
Tick-borne encephalitis	IM	3 doses on day 0, 4–12 weeks, 9–12 months	3 years	1 year	2 doses on day 0, 3rd dose day 7
Tuberculosis (BCG)	ID	1 dose after negative tuberculin test	2nd dose rarely needed	none	–
Typhoid oral	oral	4 doses; alternate days	Full course every 5 years	6 years	–
Typhim Vi/Typherix	IM or deep SC	0.5 mL once	3 years	2 years	–
Yellow fever	SC	single dose	10 years	9 months	–

Appendix 6

Vaccine Introduction and Use in Australia

BCG		
BCG	1948–	Production by CSL. School-based immunisation programs continued until mid 1980s (time varies between states).
D, T, P and Hib containing vaccines		
Diphtheria	1921	Combined toxin-antitoxin diphtheria vaccine developed by CSL. Use declined after 'Bundaberg disaster' of 1928 when 12 children died and 6 were injured by vaccine from a multidose container, probably due to staphylococcal toxic shock. This led to introduction of toxoid vaccine and single dose vials.
	1929	Diphtheria toxoid vaccine introduced for contacts of cases.
	1932–36	School-based diphtheria immunisation programs.
	1940	Infant immunisation programs began at infant welfare centres and municipal councils.
Tetanus	1939	Tetanus vaccine introduced, primarily among soldiers, with good effect – only 1 case of tetanus among 600 000 troops immunised during WW 2. Not widely used in children until DTPw vaccine available in 1953.
Pertussis	1942	Mass immunisation programs start in most states and territories.
DTPw	1953	Infant immunisation introduced, schedule varying by state and territory.
	1975	First uniform national DTPw schedule.
DTPa	1996	Vaccine registration.
	1997	Funding for 18 month and 4–5 years boosters in September 1997, except in Tasmania (October 1997) and Queensland (December 1997).
	1997–99	Funding for 2, 4, 6 month primary doses in Northern Territory and South Australia August 1997, everywhere else February 1999 except Queensland April 1999.
	2003	DTPa 4th dose at 18 months ceased September 2003.
	2011	ATAGI recommends 1st dose of pertussis-containing vaccine be brought forward from 8 to 6 weeks of age, 5th dose be brought forward from 15–17 years to 11–13 years, and consideration of reintroduction of 18 month booster dose.

dTpa	2000–03	Approved 2000, funded January 2004 to replace dT at 15–17 years. Ten-yearly diphtheria and tetanus booster recommendation was withdrawn in 2000. Free vaccine June 2009–10 for parents with an infant born from 15 June 2009 (in some states immunisation of other carers of infants is also funded).
Various DTPa combinations	1999–2003	Approval of DTPa-HB, DTPa-Hib, DTPa-HB-IPV, DTPa-HB-IPV/Hib, DTPa-IPV, DTPa-IPV-Hib; IPV recommended in 2003 routinely (in a combination) instead of OPV.
Hib	1992	Vaccine approved for children aged at least 18 months.
	1993	Hib vaccines recommended from 2 months of age, funded everywhere for infants born from February 1993.
Polio		
Polio	1955	IPV available.
	1956	IPV used in huge publicly-delivered campaign, initially to infants and young children (from January 56 to children 6 months–5 years), then progressively to adolescents and adults (ages 15–45 years) from 1958.
	1964	OPV approved after trials in Tasmania.
	1966	OPV introduced September 1966.
	2000	Western Pacific Region (including Australia) declared polio-free.
	2005	IPV (in combination) replaced OPV November 2005.
Measles, mumps, rubella containing vaccines		
Measles	1968	Vaccine approved.
	1970	Vaccine widely available.
	1975	First national immunisation schedule recommends measles immunisation at 12 months.
Mumps	1980	Vaccine approved for 1-year-olds.
Rubella	1970	Vaccine approved.
	1971	Schoolgirl rubella program (10–14 years) begins, plus post-partum immunisation of susceptible women.
Measles–mumps (MM)	1982	MM replaces measles vaccine.
MMR	1989	MMR replaces MM.
	1993	MMR for boys and girls10–16 years replaces schoolgirl rubella program.
	1998	Measles control campaign conducted. Age for second MMR dose reduced to 4–5 years.
	1999	National serosurvey demonstrates that those born between 1966 and 1980 are unlikely to have received 2 doses of measles-containing vaccine and are the most likely population group to be non-immune. MMR immunisation campaign for 18–30-year-olds.
	2000	MMR rather than rubella vaccine recommended for non-immune women of childbearing age.

Hepatitis A and B		
Hepatitis A	1993	Vaccine available from 1993. Funded for Indigenous children in north Queensland from 1999 and for Indigenous children in Queensland, Northern Territory, South Australia and Western Australia from November 2005.
Hepatitis B	1983	HB vaccine (plasma-derived) available March 1983.
	1985	Vaccine approved for neonates of HBsAg positive mothers.
	1987	rDNA vaccine recommended for at-risk adults, and infants and young children in groups with high HB carriage rates.
	1990	Funded universal neonatal immunisation introduced in Northern Territory August 1990.
	1997	Immunisation recommended for 10–16-year-olds. Programs introduced 1998–99: states with school-based programs have achieved good coverage (>80%); areas without such programs have achieved poor coverage (<20%).
	2000	Universal infant immunisation commencing at birth introduced everywhere outside Northern Territory in May 2000.
HPV		
Human papilloma virus (HPV)	2007	Introduced April 2007 for girls 12–13 years in school Year 7; catch-up for females 14–26 years until December 2009.
Influenza		
Influenza	1944	Inactivated vaccine produced in Australia.
	1968	Less reactogenic subunit or other purified vaccines used.
	2009	Funded pandemic H1N1 vaccine for ≥10-year-olds from September 2009 – December 2010; funded for children 6 months – 10 years December 2009 – December 2010.
Meningococcal		
Meningococcal C conjugates	2002–03	Available 2002, national funded program including routine infant immunisation plus catch-up up to 19 years implemented 2003 – May 2007.
Meningococcal ACWY conjugate	2010	Available late 2010.
Pneumococcal		
Pneumococcal conjugate	2001–03	Funded introduction for Indigenous children and all children in central Australia in 2001; funded for high risk children <5 years from September 2003; funded for all infants from January 2005, plus catch-up in 2005 for children born in 2003–04. 7vPCV was replaced by 13vPCV from 1 July 2011. A notional supplementary catch-up dose of 13vPCV for all children aged 12–35 months is planned till 30 September 2012. 10vPCV was used in NT between Oct 2009 and Sept 2011.
Pneumococcal polysaccharide 23-valent		Available since 1983. Funded for people ≥65 years in Victoria from 1998; funded for Indigenous Australians ≥50 years from 1999; and funded for all Australians ≥65 years from January 2005.

Rotavirus		
Rotavirus	2006	National funded program for all children born from 1 May 2007.
Varicella and herpes zoster		
Varicella	2000	Vaccine available 2001; funded vaccine introduced at 18 months with catch-up for 13-year-olds from November 2005. ATAGI recommends a second dose of varicella vaccine in the form of MMRV at 12 months of age when this vaccine becomes available.
Herpes zoster	2007	Recommended by ATAGI for all Australians ≥60 years but not funded as of Sepember 2011.
Q fever		
Q fever	1991	Limited abattoir use 1991–93; increasing coverage of large abattoirs in most states 1994–2000; funded federal immunisation program from 2001.
Smallpox		
Smallpox	1980	Immunisation ceased.

Key readings

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