Yichen Lu · Lixia Wang
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Handbook of Global Tuberculosis Control

Practices and Challenges

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Foreword

Tuberculosis (TB) is by most historical, forensic, and molecular analyses an ancient disease that dates back to the dawn of human evolution and perhaps even earlier in other animal species. Skeletal evidence of its existence has been observed in Greek mummies and its symptoms were well described in the writings of Hippocrates nearly 2500 years ago. It is not too surprising that a pathogen–host association that is measured in millennia might provide unique and unprecedented challenges for control by even the tools of modern medicine.

Over two billion people are thought to be infected by the causative organism of TB, *Mycobacterium tuberculosis*, but remarkably most of these infections are asymptomatic. Nonetheless, in the decade beginning in 2010, it has been estimated that there are 10–20 million cases of active TB in the world and that these take a toll of nearly 2 million lives a year with the developing world bearing most of this burden. While the largest number of TB cases is tallied in some of the most populous countries of the world (i.e., India, China, Indonesia, and Pakistan), many regions of the world suffer higher rates of disease due to numerous factors including feeble access to health care, poor nutrition, overcrowding, smoking, alcohol abuse, and the high co-occurrence of multiple immunosuppressive conditions.

Despite the enormous advances in our understanding of the pathogenesis of TB as an infectious disease, decades of various control measures, and new insights into factors that lead to outbreaks, we still find ourselves facing what amounts to only marginal improvements in the control of TB from a public health perspective. For example, the implementation of a TB vaccine that is now nearly a century old (BCG) has had very little measurable impact on disease incidence relative to other areas of the world that don't deploy this intervention. Antibiotic cocktails and treatment regimens that include both old and new drug combinations can work with careful compliance to suppress the disease and its transmission but are of limited use when faced with resistant variants. Together vaccines and drug therapy have only modestly slowed the evolutionary advance of *M. tuberculosis* as a formidable human pathogen. Over the last few decades, the "perfect storm" presented by the global spread of the immunosuppressive disease AIDS coupled with the emergence of multidrug resistant variants of *M. tuberculosis* has provided a new selective milieu changing the fitness

landscape of this pathogen. Although we now know the detailed genetic blueprint of multiple isolates of this bacterial organism, this knowledge has, so far, not dramatically accelerated the pace of genome-based discoveries such as the development of new TB drugs or vaccine antigens. As a scientist, I find it both alarming and humbling that the control of TB remains one of the most pressing challenges in global health despite decades of effort to identify scientific solutions to this continuing problem.

It seems the timing is right to share our collective (indeed global) experiences in areas that are important to TB control including (1) the role of vaccination, (2) strategies for early detection and diagnosis, (3) effective drug therapy and suppression of resistance, (4) transmission and outbreak control, and (5) the social and economic factors that provide a framework for success or a pathway toward failure. Thus, I read *Handbook of Global Tuberculosis Control: Practices and Challenges* with great interest and applaud the effort of the superb editorial team (Yichen Lu, Hongjin Duanmu, Lixia Wang, and Chris Chanyasulkit) and authoritative contributing authors in their assemble of this scholarly contribution. This discussion is timely and critical to our understanding of the threat that TB represents and the tools we have and need to develop to control its onslaught.

The book is organized in part through effective snapshots of individual countries that are facing the challenge of TB. This provides the reader with a myriad of different perspectives on the problem of TB control but through strategies that are shaped by cultural and historical contexts, economic constraints, and human resources. Some chapters provide customized blueprints for approaches to early detection, disease control, and prevention through the deployment of state-of-the-art technological tools. Other chapters take on the challenge of providing updates on progress toward improving public health countermeasures in the area of TB control such as new developments in TB vaccine development efforts, diagnosis in the face of vaccination with cross-reactive immunogens such as BCG, and new treatment strategies that suppress the development of resistance.

I believe *Handbook of Global Tuberculosis Control: Practices and Challenges* will be of high interest to leadership and staff of organizations that focus on public health, including governmental and nongovernmental agencies, academic institutions, research centers, hospitals, and even businesses (particularly those engaged in various aspects of addressing the TB problem). The content of the book may very likely influence the policies of such organizations, particularly those that are located within the same geographical/political spheres that represent the book's contributors.

TB is clearly an enormous problem in the developing world so understanding its epidemiology, promising new tools in its control, and all practical experiences by those facing this threat in the field are highly worthwhile aspirations for anybody interested in international development. This is important knowledge for public health practitioners, funding agencies, and all those interested in this enormous infectious disease challenge—one that has the potential to continue to undermine efforts to improve health and economic conditions for much of the world's population. I highly recommend this book to those engaged in all aspects of this critical global battle.

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Preface

This book is designed to provide a comprehensive overview of the global TB controls for public health workers, infectious disease clinicians, researchers, and policy makers worldwide. How to treat and prevent TB has challenged many generations of public health workers before us, and it will continue to challenge future generations. It is important for the current generation to see where we are today in the historical battle against this dreadful disease, how we got here, and where we are going. Unlike smallpox, which had been eradicated a few decades ago, and polio, which will be eradicated in the foreseeable future, tuberculosis infection in humans is likely to remain and spread for a long time to come. We hope this book not only helps many in the field of global TB control but also motivates more people to join in this worthy cause.

Tuberculosis is considered a controllable human infectious disease. The current TB vaccine, Bacille Calmette-Guérin (BCG), was invented more than a century ago and has been used to vaccinate millions of people every year since the 1950s, mostly in developing countries. The advent of antibiotics in the early part of the last century has converted this oldest and deadliest human infectious disease into a curable chronic disease. In fact, worldwide applications of directly observed treatment, short-course (DOTS) strategy since the 1990s have achieved unprecedented success in public health history. In many developing countries, especially in China, India, Pakistan, and Indonesia, where more than half of the global population resides, much of the modern public health infrastructure was built on the framework of government efforts to control TB.

By understanding how TB control works in these countries, readers of this book can understand their public health systems, including the organizational frameworks, disease information collection and management, and the ways in which preventive vaccines and disease treatment measures can reach cities, towns, and villages. Such a basic understanding has become increasingly important ever since the SARS epidemic in the beginning of this century, followed by the global panic caused by the spread of H1N1 Flu and the most recent Ebola crisis. The threat of a disastrous infectious disease pandemic has become so eminent that no public health worker or even world leaders can ignore it. Many believe that the current global TB

control infrastructure and experience will play critically important roles beyond TB control. Several chapters in this book describe the history of current TB control infrastructures and how they work at the national, provincial, county, and village levels. Many of these authors come from some unusual places—high up in public health, down "in the trenches"—and some of their knowledge has not been as accessible to the western world until now. It is our hope that this book can give our readers a better understanding of how public health systems function in the developing world. Different countries like China, Japan, Pakistan, and Indonesia are presented either in a country snapshot or as a case study. While these national public health systems are totally different from each other, these outstanding national public health workers have nevertheless achieved similar goals.

This seemingly "controllable" infectious disease, however, is still killing on average 4000 people a day worldwide with emerging new problems. More and more public health workers worldwide are worried about the increasing appearance of multidrug resistant (MDR) TB strains, the spread of which may take us back to the pre-antibiotics era. Combined with the new global health crisis created by HIV/AIDS in the past few decades, the unchecked spread of MDR-TB infection in immune deficient human hosts may become the worst nightmare for public health workers worldwide. Considering the more than 30 million people living with HIV/AIDS worldwide and the more than 2 billion people living with latent TB infection around the world, all public health workers and policy makers must be aware of the imminent threat of MDR-TB to global public health. Several chapters in this book specifically deal with MDR-TB with regard to various causes of treatment failures, cost and efficacy of medications, identification and care of MDR patients, and much more. The contributing authors of these chapters come from a wide range of expertise from public health policy to hands-on medical treatment. Though chapters are individually complete and the reader can select those of particular interest, taken together, they offer a comprehensive look at the current field situation of the threat of MDR-TB.

In addition to HIV/AIDS, there are other diseases that also significantly increase TB rates in populations with high latent TB infections. A chapter in this book specifically describes these TB risk factors.

With years of working experience in TB clinics treating numerous patients with suspected TB symptoms and thousands of confirmed TB patients with limited medical means available, TB clinicians worldwide would benefit from exchanging their valuable experiences and practices. Some of these TB clinicians contributed theirs in a series of chapters in this book, which can either directly help their fellow TB clinicians elsewhere in the world or provide a showcase of the routine medical practices in TB clinics to inspire academic and medical researchers to translate their laboratory research into new TB diagnosis tools, treatments, and even new TB vaccines.

Indeed, readers of this book may find it surprising that the unprecedented advancement of medical science and modern technologies in the past few decades has not translated into significant improvement of the clinical tools such as new TB diagnosis methods and TB vaccines. The century-old BCG vaccine is not used in the

United States and most of the developed world. It is still being used to vaccinate every reachable new born baby in developing countries, despite the fact that hundreds of millions of these vaccinated infants have grown into adults who still contract latent TB infections that may one day become active. The world obviously needs a new and more effective TB vaccine. Similarly, the century-old TB diagnosis method, the PPD skin test, is still being used in the majority of TB clinics and hospitals worldwide, despite the fact that almost all of the people who received the BCG vaccine in their early childhood—the majority of living populations in countries like China and India—can react positively to such a test. This technical shortcoming has made it very difficult for TB surveillance work in these countries to achieve the desired results. Through some chapters of this book that specifically discuss these issues, we hope more academic researchers will be motivated to develop advanced TB diagnosis methods, TB vaccines, and more effective treatment regimens.

Given the absence of new TB vaccines and diagnostic tools, this book includes chapters that describe how TB clinicians handle their routine challenges. For example, when dealing with a TB outbreak in close communities such as in college dorms and classrooms, local public health workers and TB clinicians have been trying to use anti-TB drugs to protect close contacts. Some people living with HIV/AIDS can also be given preventative treatment if they also have latent TB infections.

New public health workers and students often feel that securing global TB control in today's world is analogous to completing a colossal three-dimensional jigsaw puzzle: it involves multiple, complex different parts at multiple levels, and while it seems to be an attainable goal in theory, it can be nevertheless elusive in practice. From a global TB control point of view, a world map based on the reported TB cases in each country indeed looks like a mosaic plate (www.who.int). Three countries in Asia (Cambodia, North Korea, and Burma) have more than 300 cases per 100,000 people. Whereas India has the most TB cases reported in the world, the prevalence rate in India is actually in the same category as most other Asian countries such as Pakistan, Afghanistan, Nepal, Bangladesh, Thailand, Malaysia, and Indonesia. Although the prevalence rate in China is lower than in most of the neighboring countries mentioned above, China still has the second largest number of TB patients in the world. The situation in Africa is somewhat different. Almost all of the sub-Saharan countries have reported to have more than 300 cases per 100,000 people, including two of the region's high GDP countries (South Africa and Botswana); Tanzania and Angola stand out as the only two countries in the region where the reported cases rates were significantly lower. There is a country in each region—Japan in Asia and Egypt in Africa—which ranks in the lowest reported TB rate, with less than 24 cases per 100,000 people, thus representing hope for TB control in Asia and Africa. Many of us may attribute such results to the differences in each country's social and economic conditions, especially their public health and medical care systems, which obviously cannot be standardized or managed at a comparable level. But readers of this book can find a very similar mosaic picture for the TB cases reported in China, where a national standard does exist and a national public health system is functioning. There is, therefore, no "one size fits all" plan for success;

effective TB prevention and treatment programs are tailored to fit each region's particular conditions, logistics, and culture.

This book is also designed to remind us that today's global health situation is really quite far away from the goals of "an AIDS-free world" or "ending TB." It is urgently important that all governments realize the need for more investments in bilateral and multilateral programs to address TB, in particular as HIV/AIDS, TB, and malaria have been shown to be "three of the world's greatest causes of morbidity and mortality. The health crisis faced by the developing world, created by the unchecked spread of HIV/AIDS, TB, and malaria, threatens to dramatically reverse the hard-won development gains of the last 50 years" (American Public Health Association Policy no. 200322). The importance of dealing with TB as a global health priority is perhaps greater now than it ever has been—especially for the overall health and well-being of the human race. With globalization, the debilitating social and economic disadvantage associated with TB burdens on developing countries threatens our broader global society. With the prevalence of MDR-TB, the threat toward global society and its security becomes even more heightened. Finally, recognizing that we live in an increasingly interconnected and interdependent world, ending TB is truly a matter of social justice.

We thank Dr. John Mekalanos for writing the foreword of this book. Dr. Mekalanos is the Chair of the Harvard Medical School's Microbiology and Immunobiology Department, and his laboratory is engaged in the analysis of bacterial virulence and functional genomics. We truly believe that collaborative effort between medical academic researchers like Dr. Mekalanos and public health workers and TB clinicians like many of the contributors of this book can result in breakthroughs that are much needed in the field of global TB control. In the words of Dr. Gilla Kaplan, Director of the TB program at the Bill & Melinda Gates Foundation, "To accelerate progress against TB, research must be prioritized and reinvigorated. The discovery and development of new and more efficient tools and delivery strategies will be essential to achieve immediate and lasting gains against the epidemic." We present this book as a resource in this work and to facilitate transfer of information amongst researchers entrenched in this work.

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Part I

Chapter 1
Modern History of Tuberculosis Control in China

Lixia Wang

1.1 Recent History of Public Health in China

China's public health practice can be traced back to the 1930s, when Professor Zhiqian Chen and his colleagues established the first rural health pilot area in the Ding County of Hebei Province. They believed that the development of a rural health service must use a bottom-up strategy and set up a healthcare network based on the three tiers of the village, the town, and the county. However, due to Japan's invasion in the 1930s and early 1940s and the subsequent civil war, these explorations were interrupted (Guo and Guo 2007). Until 1949, the economy, science, culture, and sanitation in China were much undeveloped. Infectious, parasitic, and endemic diseases spread, and the peoples' health was seriously threatened. About 80 % of the country suffered endemic diseases, and more than 400,000,000 people were vulnerable. The death rate was greater than 2000 per 100,000 people annually, and more than half of these deaths were caused by infectious diseases. The infant mortality of newborns was 200 per 1000 births yearly. Average life expectancy was only 35 years, which was one of the lowest worldwide at that time (Chinese Health Yearbook Editorial Committee 1984; Qian 1992).

After 1949 and during the planned economy period (1949–1978), the Chinese government established the *prevention first* concept (Cai and Liu 1992; Guo 2003). The country established a disease prevention system, improved the health status in a short time, and was able to control the incidence of severe infectious and parasitic diseases. In 1952, the Soviet model of epidemic prevention and education was introduced into China, resulting in the establishment of epidemic prevention stations and schools of public health in medical universities. The newly formed public health system service focused on five major areas affecting public health: labor hygiene,

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radiation hygiene, food hygiene, school hygiene, and environmental hygiene (Wu 1996). The Chinese government began to pay more attention to the prevention and control of infectious diseases, gradually formed the prevention and control policy of government dominant multi-sector cooperation, and welcomed the participation of broader society.

Especially in the rural areas, China formed medical prevention and healthcare networks following Professor Chen's three-tier model first proposed in the 1930s: the village, the town, and the county (Li et al. 2003). From 1952 to 1982, nearly 6500 public health agencies were created within all tiers from national level to village level, and the number of health and epidemic prevention professionals increased from 22,000 to nearly 90,000 nationwide. The public health network was formed, which included health and epidemic prevention programs, local disease control programs, maternal and child healthcare departments, and frontier health quarantine programs. National tuberculosis (TB) control work was stopped from 1966 to 1976, however, due to the Cultural Revolution. Then, in 1978, the Ministry of Health (MOH) held the first national TB control conference in Liuzhou City, Guangxi Province from May 25th to June 6th.

1.2 National TB Programs

China's national programs were initially set up in a series of 10-year plans. This was intended to provide a built-in monitoring time point, in which the insured plans were based on timely data, and allowed each new plan to adapt to current public health conditions.

1.2.1 The First National TB Program: 1978–1982

In 1978, as China was transitioning to a market economy, the State Council ministry announced *The Conference Report of TB Prevention and Control Work*. The conference and report were important signs of the revitalization of China's TB control work. The report was the first document issued by the State Council on TB Prevention and Control Work since the establishment of the People's Republic of China. The report stated that China must improve the leadership and establish the TB control network. Provinces, cities, and counties should establish TB control institutions and deploy professional personnel.

During this conference, experts drafted *The National TB Control Program (1978–1985)*. Due to the lack of the reliable epidemiological data nationwide, however, conclusions were based on incomplete data, and the plan was not implemented. To resolve this problem and collect the necessary data, the MOH conducted a national TB epidemiological sampling survey in 1979. This was the first time in China's history that 29 provinces, cities, and municipalities participated in a national

TB survey. The survey provided TB epidemic baseline information, which offered the scientific basis to make plans for the following 10 years. The survey showed that the TB epidemic situation was very severe. The prevalence of active pulmonary TB (PTB) was 717/100,000 with about 7,000,000 patients with active PTB; smear-positive PTB was 187/100,000 with about 1,800,000 cases of smear-positive PTB. The rural epidemic was significantly higher than that of the city: 80 % of patients lived in rural areas and 60 % of patients were undetected and untreated. Of the patients diagnosed, 80 % could not receive effective medical treatment.

1.2.1.1 Special Projects in Direct-Controlled Municipalities

At the same time, China also launched special programs in the regions of Beijing, Shanghai, and Tianjin. These municipalities, which operate directly under the central government, took the lead in exploring the directly observed short-course chemotherapy.

Supervised chemotherapy program in Beijing. The Beijing TB prevention and control institution started supervised chemotherapy under rural conditions in 1978. At that time, the chemotherapy coverage rate was 10 % and in 1979, the smear-positive prevalence rate was 127/100,000. By 1982, Beijing carried out supervised chemotherapy in initial and retreatment smear-positive cases. For quality control, Beijing formulated a series of monitoring indicators and recorded the treatment rate and the supervised chemotherapy coverage rate of smear-positive cases, as well as the rates of qualified sputum testing, sputum negative conversion, and treatment completion. In 1982, Beijing's TB mortality rate was 11.2/100,000.

Outpatient chemotherapy management program in Shanghai. In 1981–1982, Shanghai began to execute the management of outpatient chemotherapy. A series of pilot studies were established in Fengxian County, and results looked promising.

Case detection program in Tianjin. Beginning in 1979, the government of Tianjin annually allocated special funds for the relief of PTB patients. The case detection policy in Tianjin was "symptom as the main indicator and sputum smear as the major method."

1.2.1.2 China's Public Health in 1982

During this period, the sanitary environment in urban and rural areas improved greatly due to the three-tier healthcare network and a national health campaign. The mortality rate decreased from 20 deaths per 1000 people per year (in 1949) to 6.36 in 1982, infant mortality rate decreased from 200 per 1000 live births to 34.7, and the average life span rose from 35 to 67.9 years old. Rural infectious disease death rates dropped from first in the world to fifth (MOH 2004; Liu and Rao 1984). Not only did China achieve success in controlling the mortality rate of infectious disease but it also improved the health status and life spans of its people. The World Bank (1994) regarded it as a successful "health revolution."

1.2.2 The Second National TB Program: 1982–1991

Based upon the results of the national survey of TB epidemiology in 1979, the MOH published *The National TB Control Program (1981–1990)* in 1982, which included a new TB control strategy. The program included the establishment of concrete levels of TB prevention and treatment institutions; the gradual formation of the three tiers of the TB control network; the establishment of a unified national patient registry report card, TB case registration and referral of patients; the management of detection and treatment; Bacille Calmette-Guérin (BCG) vaccination; and a media campaign. The program put forward the following objectives to reach by 1990: decrease the TB prevalence by 30 %–50 %, specifically from 717/100,000 to 400/100,000, and to decrease the smear-positive prevalence rates from 187/100,000 to 130/100,000.

This program was China's first published plan of TB prevention and control by the national government. The main principle was to adapt advanced international concepts to effectively guide national TB control work and to gradually form TB prevention and control strategies appropriate for China. This laid a good foundation for the implementation of modern TB control strategy (directly observed treatment) in the 1990s.

In order to achieve the goals of this program, a series of effective measures were put into place. By the end of 1984, 1515 TB prevention and control institutions were established nationwide, including 28 at the provincial level, 172 at the regional and city level, 533 at the county level, and the rest under the county level. Additionally, more than 30,000 professional and technical personnel were dedicated to TB prevention and control. Meanwhile, a unified national patient registry report card was introduced that standardized TB registration and reporting, and a unified TB reporting system was established by 1985. BCG vaccination work was operated in accordance with standard implementation procedures.

1.2.2.1 Special Projects in Direct-Controlled Municipalities

The application of directly observed treatment, short-course (DOTS) chemotherapy was initially explored by the MOH in Beijing, Tianjin, and Shanghai.

In order to further ensure the importance of sputum examination in TB control, the Beijing TB Prevention and Control Institution established a *Mycobacterium tuberculosis* laboratory in early 1985. By 1990, the DOTS chemotherapy coverage rate was 93 %, and the supervised chemotherapy rate of Beijing in smear-positive cases reached 98 % (Zhang et al. 1989). The smear-positive prevalence rates dropped to 16/100,000 by 1990. The mortality rate dropped from 11.2/100,000 in 1982 to 4.2/100,000 in 1990.

In 1991, local public health officials in Shanghai began to execute management of outpatient chemotherapy. The Fengxian County pilot study methods were expanded to outpatient chemotherapy programs in all districts and counties of

Shanghai. Shanghai's treatment plan was tailored to suit its size and significant traffic issues. TB control centers regularly assigned personnel to randomly check registered patients by conducting home visits, counting medications, and observing the urine color (as the color of morning urine is tinted brown when patients take rifampicin).

In Tianjin, the Health Bureau began short-course chemotherapy and developed a unified short-course chemotherapy regimen by 1984. Concerted efforts were made in Tianjin to establish a quality control system for sputum smears across the different state laboratories. In 1985, the TB work conducted in Tianjin was introduced and extended to the rest of the country.

1.2.2.2 Third National Sampling Survey: 1990

In 1990, the third national TB epidemiological sampling survey was conducted (Ministry of Health of the People's Republic of China 1992). The data revealed a TB prevalence rate of 523/100,000 persons and a smear-positive rate of 134/100,000. From 1979 to l990, TB prevalence dropped 2.8 % annually and the smear-positive rate decreased 3 % yearly. By 1990, the national TB mortality rate was 21/100,000 and the PTB mortality rate was 19/100,000.

1.2.3 The Third National TB Program: 1991–2000

Based upon results of the national TB epidemiological sampling survey in 1990, the MOH issued the second national TB control program, *The National TB Control Program (1991–2000)* in 1991. At this time, China began to carry out the DOTS strategy initiated by the World Health Organization (WHO).

The program focused on organizational leadership and legal management within the public health system. The main objectives were to strengthen the organization and management of TB control and prevention and to implement prevention and control measures as well as projects deemed necessary by the MOH. The program's objectives were to decrease the smear-positive prevalence rate by 50 % yearly and to decrease the prevalence rate to 70/100,000 by 2000.

In order to fulfill these objectives, the Chinese government undertook a series of measures in many provinces funded in part by a World Bank loan and in part by the MOH. As these methods had already been successfully tested in the special zones of Beijing, Shanghai, and Tianjin, those regions were excluded.

Measures taken during this second national TB control program were among the world's most extensive utilization of DOTS strategy. Its success made deep impacts on Chinese TB control work, especially for the successive 10 years of TB planning. A number of achievements in TB control and prevention were made from 1991 to 2000; 2,047,649 active TB cases were registered and a total of 2,004,858 cases were treated.

1.2.3.1 Fourth National Sampling Survey: 2000

In 2000, the fourth national TB epidemiological sampling survey was conducted and revealed a smear-positive PTB prevalence rate of 122/100,000, which did not achieve the goal of 70/100,000 described in the program (MOH 2002).

1.2.4 The Fourth National TB Program: 2000–2010

In 2000, on World TB Day (March 24), the WHO and the World Bank held a Ministerial Conference on TB and Sustainable Development in Amsterdam, the Netherlands. The Chinese government made a commitment to further control TB in China by formally endorsing, with 20 other countries, a declaration to take action to stop TB worldwide. Following this conference, the MOH, the State Planning Commission, and the Ministry of Finance jointly developed *The National TB Control Program in 2001–2010* which incorporated the results of the 2000 national TB epidemiological sampling survey. The program was announced to the provincial people's government, ministries, and commissions of the State Council, including autonomous regions and municipalities directly under the central government. This was the first time that the national TB control program was issued by the general office of the State Council. The State Council organized three teleconferences (in 2000, 2004, and 2006) in order to ensure that the TB control and prevention work was properly conducted.

The goals of the program were to establish government leadership and build up the joint work between the departments and society. The principles of this program were as follows: (1) to accomplish good TB prevention and control work with the help of responsible government, department coordination, and social participation; (2) to guide classification and to give priority to western areas of the nation and impoverished populations; (3) to adhere to the principle of *prevention first, combining prevention with control* in order to actively detect and treat infectious PTB patients; (4) to implement DOTS strategy and to centralize management and treatment supervision; and (5) to implement the cost policy of *pay, reduce,* and *free* and to maintain the payment-free policy for infectious PTB patients who cannot afford treatment.

In January 2002, The Chinese Center for Disease Control and Prevention (China CDC) was established. About 2 months later, the National Center for Tuberculosis Control and Prevention was established within the China CDC.

Under the national TB program, the coverage rate of DOTS reached 90 % by 2005 and 95 % by 2010. The number of infectious PTB patients treated nationally reached 2,000,000 by 2005, and the number reached 4,000,000 by 2010. Additionally, from 2001 to 2010 an estimated 8,280,000 patients with PTB were detected and treated, including 4,500,000 cases of infectious TB. The cure rate of infectious PTB was 90 %. Studies showed that if other areas of China began to implement the

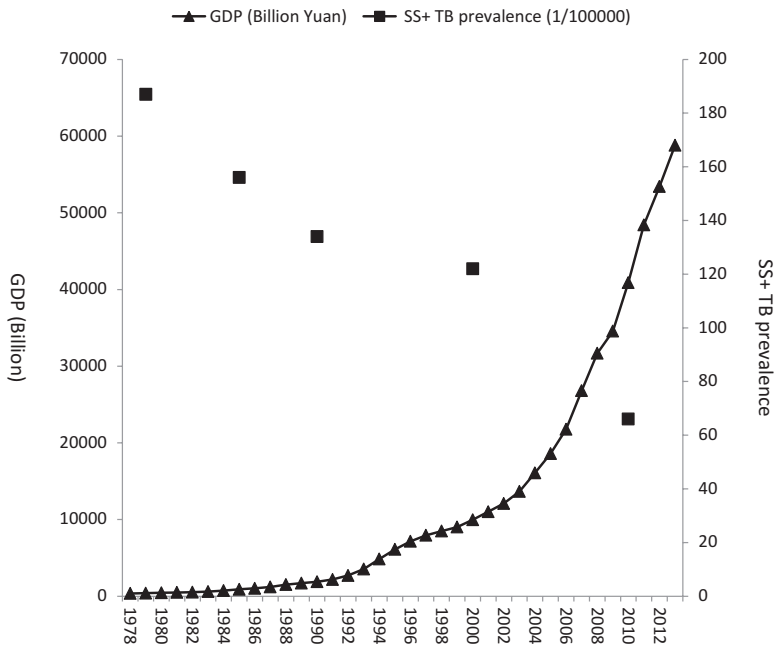

Fig. 1.1 Trends of GDP and sputum smear-positive (SS+) TB prevalence by year (China Statistical Yearbook for GDP, Report on National Tuberculosis Epidemiological Survey in China for SS+ TB prevalence)

DOTS strategy, by 2015 the smear-positive prevalence rate could be reduced by 50 %, which would achieve one of the United Nations Millennium Development Goals (Dye et al. 2002; China Tuberculosis Control Collaboration 2004).

From 2001 to 2010, 4.5 million infectious TB patients were identified and treated. This prevented an estimated two million deaths and likely reduced an annual national economic loss of 8000 million Yuan (RMB).

With the gradual increase of GDP from 407 billion Yuan (RMB) in 1979 to 40,890 billion Yuan (RMB) in 2013, the smear-positive TB prevalence dropped from 187/100,000 in 1979 to 66/100,000 in 2010 (Fig. 1.1). At the same time, the average life expectancy increased from 69 years old in 1990 to 75 years old in 2010 (Fig. 1.2).

1.3 Areas for Improvement/Continuing Challenges

The current TB control service model consists of TB prevention and treatment institutions (CDCs) providing free diagnosis and treatment; medical hospitals reporting and referring; and the community helping with suspected TB referral, treatment management, and satisfying the basic requirements of DOTS strategy. The current

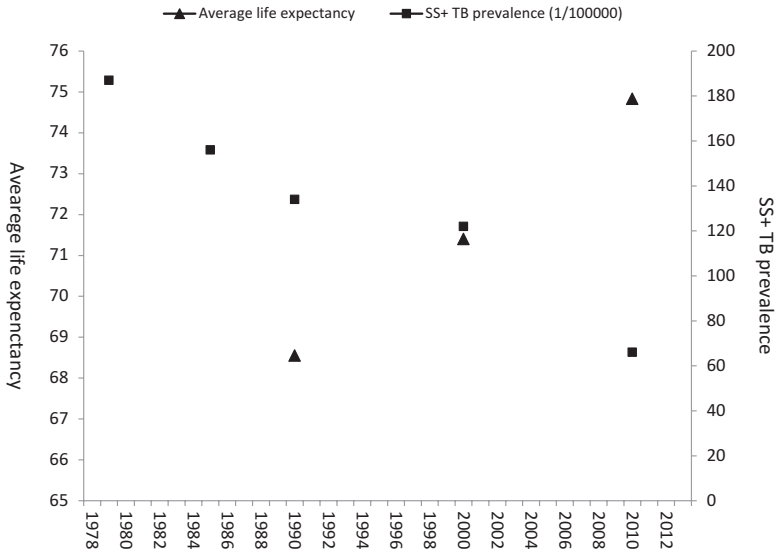

Fig. 1.2 Trends of average life expectancy and sputum smear-positive (SS+) TB prevalence by year (China Statistical Yearbook for average life expectancy, Report on National Tuberculosis Epidemiological Survey in China for SS+ TB Prevalence)

TB control system and its staff face many challenges including regional variances, securing an adequate supply of quality drugs, multidrug resistant (MDR) TB, and the need for further public education regarding TB.

1.3.1 Higher Demand on TB Prevention and Control

The regional unbalance of the TB epidemic in China increases the complexities and difficulties of TB control and prevention. According to the number of active PTB cases notified in China, 2010, the overall notification rate of active PTB was 72/100,000. However, notification rates of active PTB were lower in the eastern parts such as Beijing, Tianjin, and Shanghai and were higher in the western parts such as Guizhou, Xinjiang, and Tibet. There is a jigsaw transition pattern between the low and high rates in the central part of the country (Fig. 1.3).

Because of the regional variance, it is necessary to adjust the TB prevention and treatment service system by (1) making the TB prevention and treatment institutions responsible for planning, (2) designating medical hospitals responsible for TB diagnosis and treatment, (3) making community centers (township health hospitals) and community health service stations (village hygiene rooms) responsible for health promotion and the treatment management, and (4) formulating locally comprehensive strategies and measures for TB control and prevention which are tailored to the local regions.

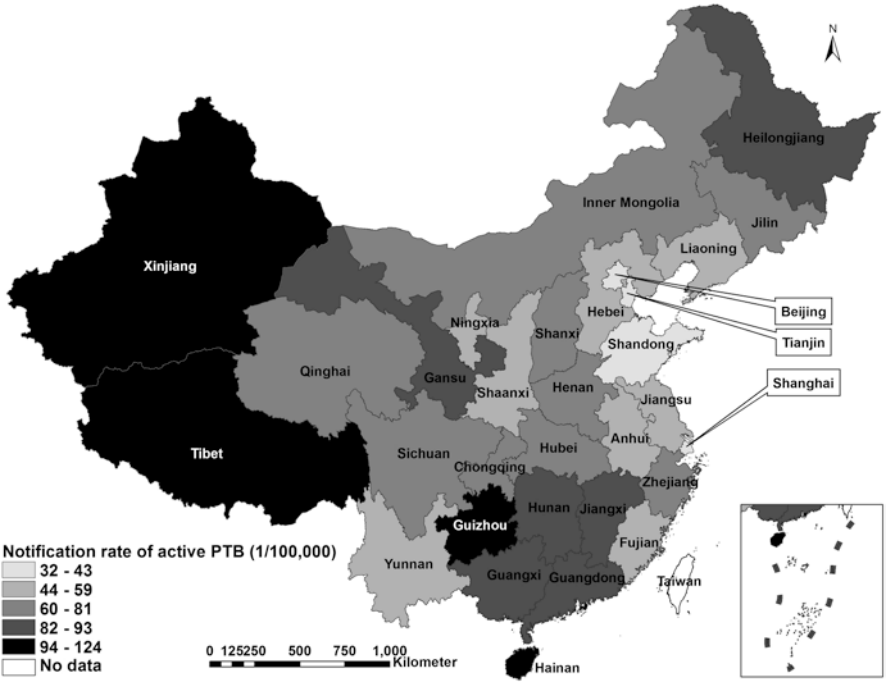

Fig. 1.3 Notification rate of active pulmonary tuberculosis (PTB) in China, 2010 (National Tuberculosis Management Information System)

1.3.2 There Is Increasing Demand for Expanded Service

The current TB control policy only provides free sputum smear examination, chest X-ray, and first-line anti-TB drugs. Patients have to pay for other related medical expenses such as monitoring of liver and kidney function, blood and/or sputum culture, treatment of adverse reactions, and other basic diagnostic and treatment items. In addition, the current TB control policies exclude certain populations such as migrant workers.

New technology, new methods of diagnosis and treatment, and improved TB case finding and whole course supervision management work (namely DOTS) should be used. Diagnosis and treatment service, including necessary routine examination, bacterial culture, and drug sensitivity testing before and during therapy, should be increased. Free treatment for adverse reactions should be provided. Also, the service should be expanded to improve accessibility for the poor and include migrants, the imprisoned, and other socially marginalized populations.

1.3.3 Funds and Policy Are Required for Multidrug-Resistant TB

The present free policy does not cover drug-resistant TB (culture, drug susceptibility testing, hospitalization, second-line anti-TB drugs, etc.). MDR TB treatment management only happens in the pilot areas, with funds from the local government and the Global Fund TB Control Project. With further socioeconomical development and the increasing demand for better healthcare, the country should include MDR TB in the national TB control program and provide policy and more financial support for MDR TB prevention and control. Toward that goal, China has been developing the relevant technical scheme for MDR TB prevention and control. *The Management Guideline for MDR-TB Control* was issued in 2012 and standardizes the diagnosis and management of MDR TB and offers technical support (Wang 2012).

1.3.4 Drug Supply, Management, and Usage Need to Be Improved

Domestic manufacturers of anti-TB drugs are few and operate at a small scale. Few second-line drugs are available. The usage of second-line anti-TB drugs is not standardized in some regions. At present, the first-line anti-TB drugs for PTB patients are combined packed; these are not fixed dose compound (FDC) as recommended by the WHO. Based upon the estimation in 2010, only 10 % of patients used FDC in China. In addition, second-line anti-TB drugs have not been incorporated into the national essential drugs list.

China should support more domestic drug manufacturers and encourage more large-scale manufacturers to produce high quality anti-TB drugs. More guidelines should be issued to ensure the quality supervision and regulation of the listed anti-TB drugs. FDC should be promoted nationwide, and second-line anti-TB drugs should be included in the national essential drugs list.

1.3.5 The Public Awareness of TB Needs to Be Improved

In 2010, the fifth national epidemiological sampling survey showed that the rate of public awareness of TB was 57 %. Some local governments and the communities have insufficient understanding of the hazards caused by TB. To improve public awareness of TB, China should make full use of a variety of resources and methods, including the observation of World TB Day (annually on the 24th of March).

1.4 Conclusion

Since the early 1990s, the Chinese government has gradually strengthened public health efforts, especially with regard to the prevention and treatment of infectious diseases such as TB. Funding and support has steadily increased yearly, and therefore TB prevalence rates have decreased. Despite such achievements and efforts, challenges still remain in preventing further spread of TB and other infectious diseases. The increase in the migrant population, the spread of drug-resistant TB, and TB/HIV co-infection remain as challenges for the Chinese government and public health.

Recognizing these challenges, the Chinese central government is attempting to make further improvements in its public health infrastructure in the nation's next 5-year development plan. In this plan, there are renewed efforts toward greater cooperation between the central health sector and local health departments and implementation of preventative measures for TB infection.

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Chapter 2
TB Control in Pakistan

Muhammad Amir Khan, Shirin Mirza, and Ejaz Qadeer

2.1 Background

Pakistan is situated in the South Asian region and covers an area of 796,096 km^2. The geographic distribution of approximately 175 million people is uneven. The annual population growth is 2.2 %, with 23 % population living below the international poverty line of $1.25 USD per day (UNICEF 2009). Pakistan has primarily an agrarian economy with almost two-thirds of its population living in rural areas. Pakistan's economic performance during the last 20 years has generally been marked by economic decline, deterioration in fiscal and current account deficits, and persistence of double digit inflation.

2.2 National Burden of Infectious Diseases

In Pakistan, the burden of communicable diseases is still high. This can be attributed to increasing rates of urbanization, overcrowding, poor sanitary conditions, and inadequate supply of safe drinking water. This is also due to lack of health education, malnutrition, and low vaccination rates (Zaidi et al. 2004). In the last 60 years, infectious diseases have remained a major cause of premature mortality and disability. Diarrhea, lower respiratory tract infections (in children), and tuberculosis (TB) have always been in the list of top ten fatal conditions in the country (Hyder and Morrow 2000).

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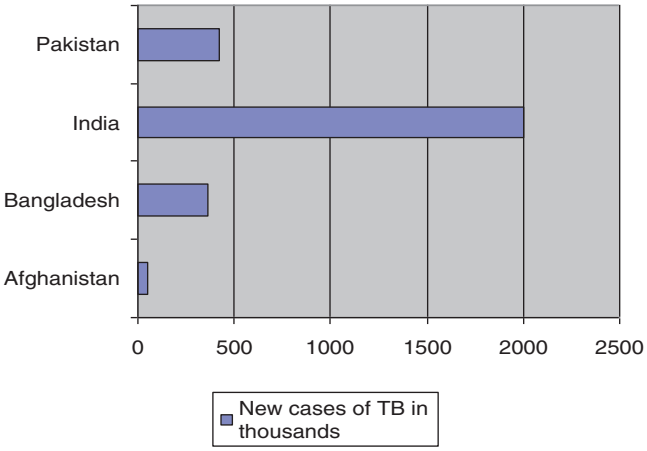

Fig. 2.1 Comparison of TB burden in Pakistan with other countries of the region

2.3 Burden of TB

The estimated prevalence of TB in Pakistan is 364 cases per 100,000 people (WHO 2010b). Pakistan stands sixth among 22 countries with a high burden of TB (WHO 2010a). In the region, the incidence of TB was highest in India followed by Pakistan, Bangladesh, and Afghanistan in 2009 (WHO 2010a) (Fig. 2.1).

In 2009, total new cases of TB reported were 258,251 and comprised 101,887 smear-positive cases, 112,948 smear-negative cases, and 43,416 cases of extrapulmonary TB (WHO 2010b). The case notification rate (CNR) both for sputum smear positive (SS+) as well as for all forms of TB and the treatment success rate (TSR) have increased over the past 10 years (National Tuberculosis Control Programme 2010).

2.4 Health Services in Pakistan

The federal government sets health policies and the provinces implement these policies for their respective populations. Health services in the public sector are provided by a number of general and specialized hospitals (965) and a network of primary healthcare outlets (595 rural health centers, 4872 basic health units, 4916 dispensaries, and 1138 maternity and child health centers) mainly under the control of the provincial department of health (Government of Pakistan 2011). Other organized semipublic sectors include healthcare institutions established and run by the armed forces, police, railways, municipal authorities, and the employees' social security institution.

The large and unregulated private sector is composed of both fully qualified and less qualified service providers in disciplines of allopathy, homeopathy, and ayurveda. The fully qualified providers include the not-for-profit non-governmental organizations (NGOs) as well as for-profit private sector institutions and individual practitioners. The private sector provides curative services to more than two-thirds of Pakistan's total population (Pakistan Federal Bureau of Statistics 2005). More than 100,000 doctors and about 33,000 nurses provide services in both the public and private heath care sectors (Akram and Khan 2007).

2.5 Public Health Interventions for TB Control in Pakistan

Since 1995, the TB Control Program in Pakistan has been unique in many ways in its response to the global and national emergency. The dimensions of unique response include the following: systematic approach to program development, strong operational research to inform program decisions, in-country working group process to adapt international program guidelines and materials, open and fair coordination with partners, and careful phasing of program interventions.

The national response to TB control challenges in Pakistan can be outlined in three phases:

- Phase I (1995–2000)
- Phase II (2001–2005)
- Phase III (2006–to-date)

2.5.1 Phase I (1995–2000)

In 1995, the government of Pakistan endorsed Directly Observed Treatment Short-courses (DOTS) strategy and formed the National Tuberculosis Control Program (NTP). This was immediately followed by the formation of the Provincial TB Control Program in each of the four provinces in the country. In these initial few years, the program focused on getting prepared for rapid countrywide implementation of DOTS. The key program achievements during the period included the following:

1. Initiation of DOTS pilots in two provinces, based on an international set of guidelines and materials. The WHO Eastern Mediterranean Regional Office (EMRO) has been the lead technical partner to assist in pilot design, implementation, evaluation, and scale-up.
2. In partnership with national and international non-governmental partners, sound operational research was carried out to inform program operational strategies. This included a randomized controlled trial to compare, under program circumstances, various options for observed treatment: facility-based, health worker

based, and family member based (Walley et al. 2001). In the same exercise, the possibility of decentralized delivery of TB care, as an inbuilt part of primary healthcare, was explored and found amenable. The research also included cost analysis and qualitative review of patients' and providers' experiences of complying with a decentralized TB care process (Khan et al. 2002). The research evidence favored patient friendly TB care rather than facility-based directly observed treatment (Walley et al. 2001; Khan et al. 2002).

3. In 1999, the program formed a technical working group with representation mainly from program staff at national, provincial, and district levels, as well as technical partners (e.g., WHO) and non-government research and development partners. During the first 2 years (1999–2000), the working group carefully reviewed the available early implementation experiences and research evidence in order to:
   (a) Formulate strategic framework for implementing DOTS in each province.
   (b) Define operational strategies for delivering TB care through district healthcare systems.
   (c) Develop a set of care providers' materials (e.g., case management deskguide and training materials for doctors, paramedics, laboratory staff, and community health workers).
   (d) Develop a set of managers' materials (e.g., district implementation planning guide, district supervision guide).
4. Start disseminating the experiences, products, and research results to international partners and programs through publication in peer-reviewed journals and international conferences.
5. Develop proposals to get federal and provincial public funding for TB control activities in various parts of the country.

2.5.2 Phase II (2001–2005)

Careful planning and preparation helped the program achieve countrywide implementation of DOTS in 134 districts and a population of more than 160 million. The activities for rapid expansion of DOTS included:

1. Public funded implementation of core implementation activities (e.g., program establishment, staff training, drugs and supplies, functioning of laboratory networks, staff supervision, recording and reporting).
2. Partner funded implementation support for core DOTS implementation. The partnerships are: (a) Fund for Innovative DOTS Expansion through Local Initiatives to Stop TB (FIDELIS) support for rapid expansion of DOTS coverage in the province of Punjab, DOTS coverage model for district headquarters and teaching hospitals, etc., (b) bilateral USAID support for expanded staff training and enhanced program monitoring, (c) bilateral Japanese International

Cooperation Agency (JICA) support for laboratory network strengthening and establishing four model districts in Punjab.
3. Bilateral partner funded set of activities to develop a strategic framework and an intervention design for developing public–private partnerships. This led to the development of an innovative district-led approach, in which the district health office plays a lead role in supporting selected private clinics and hospitals to deliver quality TB care, as per national guidelines.
4. The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund) funding support (through Rounds 2 and 3) to (a) develop pilot studies and evaluations in five metropolitan cities, the franchise model of developing a public–private partnership for TB control, (b) strengthen and support two networks of NGO clinics for delivering quality TB care, (c) enhance program capacity for implementing behavior change communication, (d) develop, pilot, and evaluate interventions for grassroots level advocacy and community mobilization, including social rehabilitation of TB patients, in 20 districts of Pakistan, and (e) pilot childhood TB interventions in a few selected districts.
5. Continued operational research and program development activities, mainly in partnership with (a) non-government research and development partners (both national and international), through international research consortiums and grants, and (b) program staff in research support unit and field operations, through regional TDR (WHO) and other research grants.
6. These rapid expansion efforts of the program and its partners led to 100 % DOTS coverage in public sector facilities in 1145 diagnostic centers and 5000 treatment centers by the end of 2005.

2.5.3 Phase III (2006–to Date)

This phase refers to a set of program activities for sustaining the country wide public sector DOTS coverage, improving the quality of ongoing care, and expanding into other components of the Stop TB Strategy Pakistan (adapted from the Global Stop TB Strategy). The national strategy has six principal components:

– Pursuing high-quality DOTS expansion and enhancement
– Addressing TB/HIV, MDR-TB, XDR-TB, and other challenges
– Contributing to health system strengthening
– Engaging all care providers
– Empowering people with TB and communities
– Enabling and promoting research

Now, we look at the progress made in each of the six strategic components.

2.5.3.1 Pursuing High-Quality DOTS Expansion

1. The program currently, through a technical working group process, is updating the operational policies and care delivery materials (such as desk-guide and training materials) in light of new developments during the last 10 years.
2. The program, mainly through The Global Fund Round 6 support, established a district-based external quality assurance for 1145 public laboratories with one at each diagnostic center in the country. One national, four provincial, and two regional reference laboratories are also strengthened for an enhanced role in training of laboratory staff and supporting the external quality assurance in the respective province or region.
3. Mainly through public funds and The Global Fund Round 8 support, the program arranged the resources to provide free anti-TB drugs of proven quality to TB patients in all parts of the country. The program and its partners are currently implementing drug management improvements, including staff training and enhanced storage and distribution of anti-TB drugs.
4. The program developed and introduced operational guidelines for structured monitoring events at facility, district, and province levels. The program field monitoring capacity has been enhanced through a team of qualified Program Officers, each responsible for supporting a cluster of four to five neighboring districts.

2.5.3.2 Addressing TB-HIV Co-infection

1. Current HIV prevalence among the general population is less than 0.1 % (Government of Pakistan 2009) with unsafe sex and needle sharing as predominant modes of transmission.
2. A national level board has been constituted to steer the program's coordinated work for TB-HIV co-infections and MDR-TB.
3. The existing HIV Treatment and Care centers are being enabled (through The Global Fund Round 6) to manage TB screening and care for TB-HIV co-infected cases. The enabling of these centers includes: staff training, infection control measures, provision of materials, referral linkages, and monitoring support.
4. The TB Control Program (through Global Fund Round 6 support) has also started HIV-screening of TB patients at about 20 sentinel sites (i.e., TB diagnostic centers). When possible, those found co-infected with TB and HIV will be managed for TB-HIV co-infection at the nearest HIV Treatment and Care Center.

2.5.3.3 Addressing MDR-TB

1. The WHO estimated annual incidence of culture positive and all types of MDR-TB in Pakistan are about 7939 and 13,280 cases, respectively (WHO 2009).

2. The program has managed to get the Green Light Committee (GLC) approval for MDR-TB care at selected teaching and specialized hospitals (both public and private). With WHO and the Pakistan Chest Society, the program has also developed the national technical guidelines for managing MDR-TB cases in Pakistan.
3. Early implementation experiences at a few public and private hospitals provided the national program a basis for developing operational strategies to deliver community-based (i.e., decentralized) care to MDR-TB patients. The package of patient care also includes social support in the form of food baskets and travel reimbursements.
4. The program, with partners' support, developed guidelines and training and communication materials for various staff categories working at teaching hospitals and at the peripheral clinics. The technical content is based mainly on international materials by the World Health Organization (WHO) and Partners in Health (PIH), whereas operational content reflects the national program operational policies. These operational materials, the first of their kind, will impart practical knowledge and skills for delivering MDR-TB care, as per national guidelines. The guidelines and materials are being piloted and evaluated at selected sites before scaling up to countrywide distribution by the end of 2015.
5. The program has secured The Global Fund funding (Round 9) for a 5-year plan to scale-up MDR-TB care through 30 teaching and specialized hospitals and more than 2500 DOTS-Plus clinics, including both public facilities and private clinics/hospitals. These selected hospitals and DOTS-Plus clinics will be strengthened and supported for provision of MDR-TB care as per national guidelines.
6. The program, through The Global Fund and bilateral support, is already reinforcing six provincial/regional and one national reference laboratories for drug sensitivity testing and technical support as well as 15 hospital-based culture laboratories for culture and rapid diagnostic testing of MDR-TB.

2.5.3.4 Other Challenges

1. The program developed the Childhood TB treatment guidelines (technical) in partnership with the Pakistan Pediatric Society. These treatment guidelines have been piloted and evaluated in a few selected districts through The Global Fund support (Safdar et al. 2010).
2. In light of early implementation experiences, the program developed the case management desk-guide and training materials for health staff working at hospital outpatient facilities. These guidelines and materials are currently being implemented in about 28 teaching and specialized hospitals (through The Global Fund Round 6).
3. By 2015, the childhood TB care interventions will be expanded countrywide to the district and subdistrict level hospitals.
4. The program has also initiated efforts to improve the diagnosis and treatment of extrapulmonary TB cases. Staff at all the teaching and specialized hospitals are

being enabled to follow national guidelines for managing extrapulmonary TB cases. The intervention will gradually be expanded countrywide to all district headquarter hospitals.

2.5.4 Contributing to Health System Strengthening

The program has been encouraging innovations for enhanced case finding and case holding interventions for various hard-to-access population groups. The country has already received four TB REACH grants in the first two waves for developing, piloting and evaluating innovations.

2.5.4.1 TB-Tobacco Interventions

1. The program is currently supporting non-government partners in conducting a randomized controlled trial to compare the effectiveness and feasibility of using counseling and chemicals (medicine) in tobacco cessation interventions. The WHO five steps to quit program forms the basis of the cessation process being tested. A specially designed communication tool has been developed to assist in counseling. A cost analysis study and a qualitative study will help in explaining the trial results and experiences and informing the program decisions to expand tobacco cessation intervention in other parts of the country (Siddiqi et al. 2010).
2. The program, with non-government partners, is also working on developing, piloting, and evaluating a smoke-free home intervention for known TB cases.

2.5.4.2 Lung Health Interventions

1. With partners, the program has started preparing for countrywide interventions on lung health conditions other than TB. These conditions include asthma, chronic obstructive pulmonary diseases, and acute respiratory infections.

2.5.5 Engaging All Care Providers

1. The program, through The Global Fund and other support, has enabled multiple countrywide and regional networks of non-governmental clinics for delivering quality TB care. The enabling mainly included: (a) initial assessment and planning, (b) material support, e.g., drugs, supplies, print materials, microscopes, (c) supplemental staff for delivery and management of TB care, and (d) technical inputs to help develop operations and systems. These enabled non-governmental

clinics provide quality care to 10–15 % of the registered TB patients in the country.
2. In light of early experiences with "franchise" and "district-led" approaches to engaging private clinics/hospitals, the intervention is currently being expanded (through The Global Fund Round 9) to 60 districts of Pakistan. The expansion is based on a set of program materials developed in the past few years of early implementation (see Phase II for details).
3. The program is also working with networks of government-owned hospitals (e.g., social security, railways) and departmental health facilities (e.g., prisons) for expanded DOTS coverage to their respective populations.

2.5.6 Empowering People and Communities with TB

1. The program developed the strategic framework and set of operational guidelines and materials for various people-empowering activities. These activities have four main pillars:
   (a) *Advocacy*: public relations, lobbying initiatives, and advocacy to influence decision makers, opinion leaders, and partners.
   (b) *Communication*: advertising, media, promotion through branding.
   (c) *Social mobilization*: community events and community groups.
   (d) *Patient empowerment*: innovations such as social support, rehabilitation, and health insurance of patients and families that need to be assessed and considered for scaling-up.
2. The program is working on expanding the advocacy, communication, and social mobilization activities in the remaining 77 districts (i.e., only 57 districts are currently supported through The Global Fund Round 6). This also includes piloting and evaluating people-empowerment innovations for potential future expansion.

2.5.7 Enabling and Promoting Research

1. The program realized the importance of operational research in informing the operational policies. The program has demonstrated the value-addition of research and development investments into program interventions, and the staff is committed to continuing and expanding its research enabling and promotion efforts. See Phases I and II for examples of operational research contribution to the program.

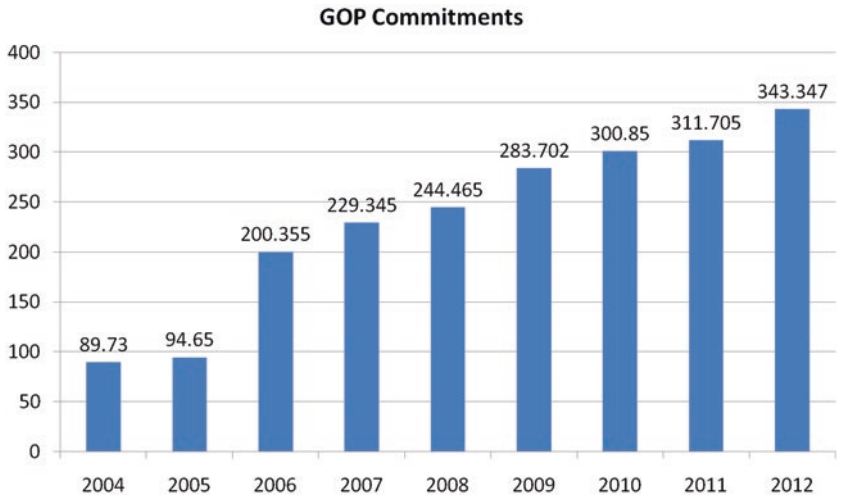

Fig. 2.2 Government of Pakistan (GOP) Financial Allocation for National TB Control Program 2004–2012 (in Million Pakistan Rupees)

2.6 Lessons Learned

1. The high level of government and partners' commitment, reflected in the exponential increase in the financial commitment during the last few years, has been key to the program's rapid expansion and achievement of consolidation targets (Fig. 2.2).
2. Investment in long-term partnership development with international and national partners, based on mutual understanding and trust, gives higher performance dividends. The program's ability to coordinate with multiple partners and to maintain openness and fairness in respective relationships plays an important role in strengthening its functions and structures. In assessing and documenting its technical assistance needs, the program can help in encouraging partners to openly discuss and plan their contributions in areas of mutual interest.
3. International guidelines and materials are a useful basis for the country program to adapt to their local context. The use of context-adapted operational guidelines and materials makes it easier for the healthcare staff to deliver care as per the national guidelines.
4. The program always faces multiple pressures for rapidly expanding the interventions. This sometimes poses risks to the preparations required for effectively scaling-up the intervention. The manager's ability to manage a balance between "adequate preparation" and "quick coverage" can play an important role in the success and sustainability of program interventions. Research and development work embedded into an early implementation of program interventions can give more timely and valid information and products for expansion decisions.

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Chapter 3
TB Control in South Africa

Halima Dawood and Nesri Padayatchi

3.1 National History and Current Status of Infectious Diseases in South Africa

In sub-Saharan Africa, the majority of the country's health resources are utilized in the management of infectious diseases to deal with the burden of human immunodeficiency virus (HIV), tuberculosis (TB), and malaria. The focus has mainly been on treatment rather than the prevention of infectious diseases (Daar et al. 2007).

The HIV epidemic, in tandem with tuberculosis, continues to shape healthcare in the public sector in sub-Saharan Africa including South Africa. Infection with HIV increases the risk of other infections with resultant increased morbidity and mortality associated with communicable and noncommunicable disease. Scale-up of antiretroviral therapy (ART) has led to the creation of chronic infectious disease treatment programs and has produced new innovative methods to deliver healthcare to a large number of individuals. By the end of 2008, four million people in low- and middle-income countries of which 730,000 are from South Africa had commenced ART (WHO 2009a). Antiretroviral treatment programs have focused on the treatment and management of HIV infection (in as many individuals as possible) and the short-term complications of ART. As a result, integration of HIV care with other services, TB care in particular, has been lacking.

The South African HIV counseling and test campaign is the first step in a comprehensive approach to screen not only for HIV infection but also for hypertension, diabetes, anemia, and TB. However, in order for this campaign to be successful, it

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requires health system strengthening to ensure that individuals who require interventions are able to link to these services immediately.

A life course approach to disease prevention, looking at the entire health experience of individuals and families rather than focusing on one or a few diseases, is urgently needed. People face daily interconnected risks. While there are biological risk factors for diseases, people have common risk factors that may be addressed with an efficient public health approach.

3.2 National Healthcare History, Practice, and Spending in South Africa

Prior to 1994, the South African healthcare system was fragmented. Service delivery was divided according to race with minimal attention to the health-specific needs of women and children. Colonization and apartheid policies resulted in dispossession and poverty amongst the nonwhite population. Income inequalities and the migrant labor system resulted in the destruction of family life with resultant social changes (Coovadia et al. 2009).

Following the birth of democracy in South Africa in 1994, there was substantial restructuring of the public health sector that ensured access to healthcare for all citizens and more equitable health resource distribution between the geographic areas. On the 24th of May 1994, President Nelson Mandela declared that all healthcare for pregnant women and for children under the age of 6 years would be provided free to citizens at public health facilities. This free primary care policy was extended to all public health facility users starting on 1 April 2006.

In 1994, a district-based healthcare system was established that would be more responsive to local needs delivering primary healthcare (Owen 1995). However, these transformations have been challenged by the increasing burden of disease related to HIV/AIDS and TB, the failure to devolve authority fully to local districts, and lack of efficient and equipped staff. This has resulted in poor service delivery and poor health outcomes relative to total health expenditure (Harrison 2009).

The South African healthcare system is characterized by a public sector system, a predominantly nurse-based delivery of primary healthcare financed by general tax revenue, and a private healthcare system, dominated by medical schemes (insured) and a small proportion of self-funding (Blecheri and Harrison 2006). The current healthcare expenditure for the uninsured population in South Africa is 3 % of gross domestic product (GDP). Spending on the ART program is estimated to reach 40 % of the total health budget by 2020, compared with 12 % today (Cleary 2009). To achieve 80 % coverage in the ART program in the next decade, spending for healthcare will need to be increased from 3 to 5 % of GDP.

Plans are under way to implement a proposed National Health Insurance (NHI) system. This is an attempt to provide a different financing system for healthcare and improve access to public resources and health services.

3.3 National Strategy with Regard to Research Support and Spending in South Africa

A national program for TB control in South Africa has existed since 1979 but service delivery was vertical and fragmented. There were 18 health authorities of various "home affairs" for different races and "homelands" and "independent" states. The management of these fragmented TB services was complex and rendered the program unmanageable and dysfunctional (Edington 2000). While TB was a notifiable disease and accounted for the majority of disease notifications, the case definition for notification was ill-defined and the majority of cases were diagnosed using chest radiographs. Tuberculosis patient outcomes were reported in three categories: cured and discharged, absconded, or deceased. As a result, between 14 and 92 % of individuals were recorded as completing TB therapy. Lack of access to health facilities, especially in rural settings, resulted in underdiagnosis of tuberculosis. TB treatment was restricted to in-patient management, which resulted in long periods of hospitalization.

In 1994 an appraisal of the South African National Tuberculosis Program (NTP) found that there was lack of implementation of the policy and inadequate focus on infectious smear-positive TB cases. In addition, there was a maldistribution of hospital beds and laboratory services, and the information system was inadequate for evaluation and monitoring. Following this review a new TB recording and reporting system was implemented (Edington).

The national TB review in 1996 revealed that while there were sufficient financial resources (R500 million), a reliable drug supply, and acceptance of the directly observed treatment, short course (DOTS) strategy, there was a lack of efficient management of resources at all levels of care and the DOTS strategy was incompletely implemented. TB registers were incomplete and laboratory services were insufficient for diagnosis of tuberculosis.

3.4 The Historical and Current Comparative Scale of the TB Epidemic in South Africa

There were an estimated 9.4 million (range 8.9–9.9 million) new cases of TB globally in 2009 with an annual mortality of 1.7 million (WHO 2009b). This is an increase from 8.3 million cases in 2000 and 9.3 million cases in 2007. Of the 9.4 million incident TB cases in 2008, 30 % occurred in Africa and 55 % in Asia. The five high-burden countries, ranked according to highest absolute number of incident cases, are India (1.6–2.4 million), China (1–1.6 million), South Africa (0.38–0.57 million), Nigeria (0.37–0.55 million), and Indonesia (0.34–0.52 million) (Andrews and Pillay 2005).

Tuberculosis is a major public health issue in South Africa and contributes significantly to mortality in HIV-infected individuals. South Africa is committed to

meeting the millennium development goal (MDG) six target of halting and reversing the incidence of TB by 2015. Following the inception of the revised NTP in 1996, there was an improvement in the case detection rate (CDR) for new smear-positive TB cases over 100-fold from 6.7 % in 1997 to 78 % in 2007. However, there was only a 6 % improvement in CDR between 2005 and 2007. South Africa has exceeded its target CDR of 70 %, mainly due to the increase in DOTS coverage in the country and a greater number of on-site and district laboratories.

The emergence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) further complicates the management of TB control programs. Cases of XDR-TB have been identified in all nine provinces in South Africa (Andrews and Pillay 2005).

3.5 Effective Public Health Measures: Lessons and Successes

One of the strengths of the tuberculosis program in South Africa is that TB is a notifiable condition. However, despite strong population-based vital registration systems, TB treatment interruption rates and mortality remain high. This is attributable to the high HIV infection burden, socioeconomic challenges, and weak healthcare service delivery mechanisms.

For new smear-positive TB cases, the treatment success rate improved from 60 % in 1999 to 74 % in 2006 but still remains below the national target of 85 %. There is heterogeneity in treatment cure rates across the provinces. Published data from 2006 show rates ranging from 53 % in KwaZulu-Natal to over 77 % in the Western Cape. While the incidence of new smear-positive cases has not increased substantially from 1993 to 2007 (Fig. 3.1) there is a high rate of smear-negative TB among the HIV infected. This increases tuberculosis-associated complications.

DOTS needs to be implemented in a more innovative, patient-centered program. Many TB patients are required to attend clinics daily in order for treatment to be observed or else the patients get no treatment support at all. The HIV treatment program has dedicated time and effort to focus on adherence education and checks. There is an urgent need for community-based and patient-centered adherence programs that are convenient and acceptable to patients with TB.

There has been substantial progress in increasing capacity to diagnose and treat sensitive, MDR-, and XDR-TB. South Africa is one of the few countries on the continent with this capacity, as reflected in the World Health Organization (WHO) indicators used to assess the management of drug-resistant TB (Table 3.1). By 2007, South Africa had conducted drug resistance surveillance, developed national guidelines and training material, conducted training, initiated treatment scale-up, fully integrated the drug-resistant TB program into activities of the NTP, and reported MDR-TB data (WHO 2009b).

The South African NTP has decentralized the management for MDR-TB. Centralized MDR-TB units (one in each province) are responsible for initiating and monitoring treatment of MDR- and XDR-TB cases in addition to

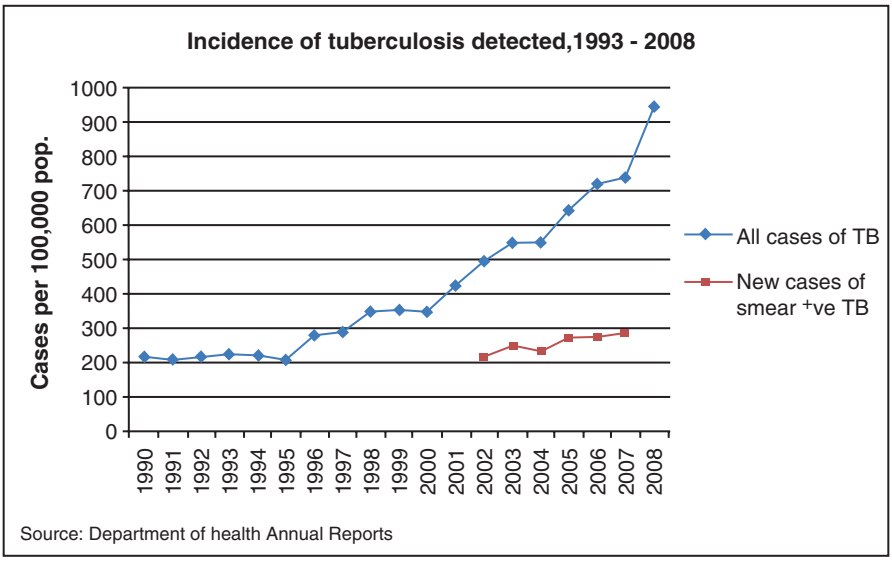

Fig. 3.1 Incidence of detected tuberculosis in South Africa, 1993–2007

Table 3.1 Number of MDR-TB cases estimated, notified, and expected to be treated, in the four highest MDR-TB burden countries

	Estimated MDR-TB cases		Notified cases		Expected MDR-TB cases to be treated	
	2007		2007		2007	2008
Country	% of all TB cases	No. of cases	% of estimated cases	No. of cases	No. of cases	No. of cases
India	5.4	130,526	0.1	99,639	146	450
China	7.5	112,348	0.1	76,154	79	388
Russian Federation	21	42,969	17	31,397	5297	4221
South Africa	2.8	15,914	69	10,708	7350	5252

Adapted from *Global Tuberculosis Control: Epidemiology, Strategy, Financing: WHO Report 2009*

providing support to the decentralized satellite MDR-TB units within that province. The decentralized MDR-TB units initiate and monitor treatment of only MDR-TB cases. Mobile MDR-TB clinics and community supporters provide treatment and support to MDR-TB patients after they have been stabilized from both the decentralized and satellite units.

While this increased capacity to diagnose and treat TB is to be commended, more effective mechanisms that extend beyond healthcare delivery are urgently required to improve the control of tuberculosis. Social and economic drivers that increase the risk of infection need to be considered in the TB control program.

3.6 Identifying Risks and Worst-Case Scenarios

Risks to a successfulTB control program in South Africa include failure to reach national targets, high treatment interruption rates, unsatisfactory follow-up of individuals lost to follow-up, late presentation of patients to health facilities for care, inadequate active case finding, substandard infection control practices, insufficient community engagement, lack of integration of TB and HIV services, poverty, overburdened health infrastructure, increased levels of MDR-TB, and emergence of XDR-TB.

3.7 Urgent Needs and Action Steps

There is an urgent need to improve TB control programs and treatment for both susceptible and drug-resistant tuberculosis. Laboratory capacity (beyond centralized laboratories) with point-of-care testing and treatment is the key to effective management of infectious diseases as illustrated by malaria and HIV testing and treatment programs. The primary drivers of tuberculosis and the HIV epidemic are economic and social inequalities. Service delivery to improve sanitation, clean water, and housing, together with healthcare infrastructure, education, and employment, is paramount not only for TB control but also for the management of other infectious diseases to reduce the opportunities for infectious disease spread. This would require intersectorial collaboration and interventions that address the social determinants of health and is likely to impact other chronic diseases.

South Africa has adopted the Stop TB Partnership Policy of the three Is:

- Intensified case finding
- Isoniazid prophylaxis for latent TB
- Infection control.

These are in varying phases of implementation and have yet to be optimally implemented and evaluated. We recommend that a fourth "I" be added: "Integration of TB and HIV management."

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Chapter 4
Tuberculosis Control in Hong Kong

Kwok Chiu Chang and Cheuk Ming Tam

Abbreviations

DOT	Directly observed treatment
DOTS	Directly observed treatment, short course
DST	Drug susceptibility testing
HIV	Human Immunodeficiency Virus
LTBI	Latent tuberculosis infection
MDR-TB	Multidrug-resistant tuberculosis
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

4.1 Current Status of TB in Hong Kong

Tuberculosis (TB) was first listed as notifiable in Hong Kong in 1939. Not only is TB one of the 47 statutory notifiable diseases in Hong Kong under the Prevention and Control of Disease Ordinance, it is also one of the 48 prescribed occupational diseases in Hong Kong under the Employees' Compensation Ordinance. TB surveillance is done through a statutory notification system. Data from the TB Reference Laboratory (under the Department of Health) and death certificates are regularly matched with the TB notification registry to trace back unreported cases.

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With a smear-positive case notification rate between 5 and 50 per 100,000 population, Hong Kong has been classified by the World Health Organization (WHO) under countries or places with intermediate TB burden with a good infrastructure (WHO Western Pacific Regional Office 2002a). The TB notification rate in Hong Kong has substantially declined from 113.7 per 100,000 population in 2000 to 72.5 per 100,000 population in 2010 (Fig. 4.1), with a low TB death rate of 2.7 per 100,000 population in 2010. Alongside the decline in TB incidence was a significant decline in drug resistance rate (Kam and Yip 2001, 2004). Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) constitute around 1 % and 0.1 % of culture-positive TB, respectively. Approximately, 1 % of TB patients are HIV infected (Department of Health 2013).

The public TB control program in Hong Kong is fully funded by the government. The bulk of TB care is delivered by the TB and Chest Service of the Department of Health through 18 chest clinics (12 full time and 6 part time) which are free of charge and easily accessible to citizens. Introduced in Hong Kong on a trial basis in the early 1960s, TB treatment supervision in the outpatient setting has become a routine practice since the 1970s. Of the 5093 notified TB cases in Hong Kong in 2010, approximately 80 % were managed under the TB and Chest Service (Department of Health 2013). Both first- and second-line anti-TB drugs are provided free of charge. Hospital beds for TB are provided mainly in five public chest hospitals. Other health facilities may also care for TB patients, especially those with multiple medical problems. Citizens also have the freedom of choice to seek services from the private sector. Collaboration and coordination between different healthcare providers are actively promoted through a central coordinating committee convened by the Department of Health in collaboration with the Hospital Authority.

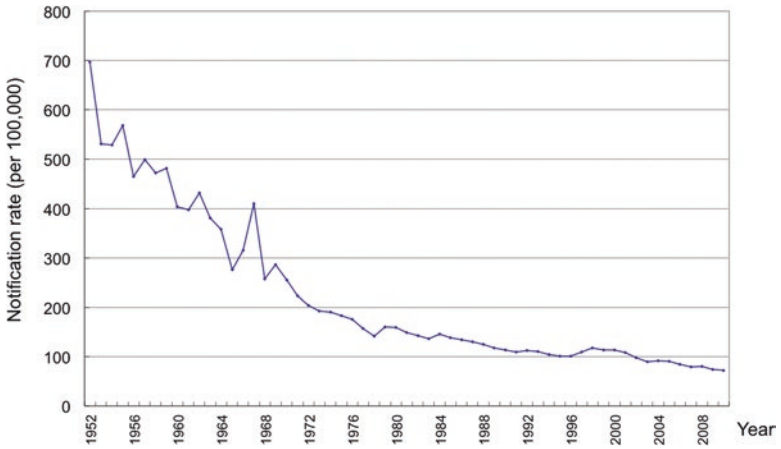

Fig. 4.1 TB notification rate in Hong Kong, 1952–2010

4.2 TB Control Measures

To reduce morbidity and mortality, stop new infections, and prevent progression from infection to disease, the TB control program in Hong Kong comprises five core components: case finding, effective chemotherapy, treatment of latent TB infection (LTBI), BCG vaccination, and health education.

4.2.1 Case Finding

4.2.1.1 Passive Case Finding

Passive case finding, which refers to picking up diseases in symptomatic patients seeking treatment, has been the mainstay of the local case-finding activities. This is in line with evidence in the WHO TB control strategy (WHO 1974) and published literature (Chang et al. 2009; Meijer et al. 1971; Toman 1976). A walk-in approach has been employed by the chest clinics. Free diagnostic and treatment services are offered at multiple convenient sites by the 18 chest clinics.

4.2.1.2 Active Case Finding

Active case finding refers to the screening of subjects at risk of having TB disease or progression from LTBI to TB disease. These subjects include household contacts of TB patients, immigrants and refugees from countries with a high TB incidence (British Thoracic Society 1994; Rieder et al. 1989), marginalized populations (Friedman et al. 1987), and inmates of correctional services (Anderson et al. 1986; Leung et al. 2005). Given incomplete data regarding high-risk groups, a low proportion of TB cases in Hong Kong attributable to recent immigrants, as well as limitations of current diagnostic tools for LTBI, active case finding in Hong Kong is currently focused on household contacts, HIV-infected subjects, and silicotic patients. Even among the household contacts, a commonly recognized high-risk group, the yield of TB disease within 5 years is on the order of 1–2 % (Lee et al. 2008).

4.2.1.3 Mass Screening

Mass chest X-ray screening was abandoned in Hong Kong in the mid-1970s upon recommendations of the WHO (1974) in line with the demonstration of its low cost-effectiveness in a series of studies (Balasangameshwara and Chakraborty 1993; Mangura and Reichman 1999; Meijer et al. 1971; Toman 1976). A local study has also demonstrated that chest radiography is not useful in screening for active TB disease in asymptomatic HIV-infected patients (Ho et al. 1999).

4.2.2 Effective Chemotherapy

Of all TB control measures, effective treatment of infectious TB patients is the most important component. Non-adherence is the most common cause of treatment failure. Supervised TB treatment was introduced on a trial basis in the 1960s in response to a treatment completion rate of about 25 % and mounting drug resistance (Department of Health 1975) and has been routinely delivered in all chest clinics in Hong Kong since the 1970s. The implementation of supervised treatment was later facilitated by the advent of intermittent regimens and short-course treatment in 1979 (Fox et al. 1999; Mitchison 2005). In the early 1990s, supervised treatment became widely renamed "directly observed treatment (DOT)" (Bayer and Wilkinson 1995). This is a core component of a five-component control strategy known as directly observed treatment—short course (DOTS) which is recommended by the WHO in response to the global resurgence of TB disease in the late 1980s and early 1990s (WHO Western Pacific Region 2005).

The coverage of DOTS in Hong Kong is essentially 100 %, as it is accessible to every Hong Kong citizen. The cost of DOTS is justifiable in view of the higher cost of the consequences of unsupervised treatment: a higher risk of disease morbidity and mortality; treatment failure; relapse; and acquired drug resistance, especially the MDR-TB and XDR-TB that have emerged in many communities worldwide (WHO 2010).

In Hong Kong, DOTS has been promoted through affordability, availability, accessibility, and acceptability. TB-related medical services are delivered free of charge. Although an appointment system has been introduced in the last decade to reduce waiting time before consultation, the historical walk-in system that provides for consultation without a prior appointment has been partially preserved to enable rapid management of patients at high risk of active TB. DOT is provided through extended working hours. A total of 18 chest clinics serve different parts of the territory. Patients can attend any chest clinic for DOT. A "mutualistic" approach (Stewart and Roter 1989), which emphasizes involving the patient in the plan of patient management, has been advocated in the delivery of care.

Treatment outcomes are monitored regularly. According to the WHO, the DOTS case detection rate in Hong Kong for new smear-positive cases in 2009 was estimated to be 89 %, which is higher than the WHO's targeted detection rate of 70 %. Treatment success rate at 1 year for the 2008 cohort of new smear-positive cases under DOTS was 78.5 %, while at 2 years, it was significantly higher at around 85 %, the WHO's target for treatment success rate.

Hong Kong has also implemented DOTS-Plus with widely available drug susceptibility testing (DST). DST against second-line drugs is done in the presence of bacillary resistance to two or more first-line drugs. Rapid culture in liquid medium and molecular tests for rifampicin resistance are available for cases at risk of MDR-TB. Second-line drugs are accessible for individualized TB treatment according to DST results. The TB Reference Laboratory of the Department of Health in Hong Kong, which has been formally designated by the WHO as one of the Supranational Reference Laboratories since February 2006, actively participated in the WHO/IUATLD Global Project on Anti-TB Drug Resistance Surveillance (WHO 2010).

Despite the implementation of DOTS, treatment non-adherence, which is notorious for its poor predictability (Chang et al. 2004; Fox 1958, 1962; Sbarbaro 1990), still occurs for various reasons including human rights claims. Default, defined by the WHO as treatment interruption for at least 2 consecutive months (WHO Western Pacific Region 2005), represents an extreme case of non-adherence. The treatment defaulter rate in Hong Kong was 4–5 % (4 % among new cases and 8.5 % among retreatment cases) (Department of Health 2002), and about 5–6 % in a relatively recent cohort (Department of Health 2013). A defaulter tracing system is in place to trace every patient by phone call and mail, and by home visit if necessary, as soon as a patient misses one dose of medication. Defaulter tracing requires good communication skills with patience and a friendly attitude. Education, counseling, and social or financial support are often needed. Hospitalization may be required. Coercive measures are seldom considered in Hong Kong on balance of their pros and cons.

4.2.3 Treatment of LTBI

Currently, screening and treatment of LTBI are mainly targeted to close contacts of smear-positive index cases, the HIV-infected, and silicotic patients. Ongoing evaluations are being made to assess the efficacies of such interventions.

4.2.4 BCG Vaccination

BCG (Bacille Calmette-Guerin) vaccination was first given in Hong Kong in September 1950 (Lee 1950). Newborns are now vaccinated mainly in the hospital at birth. The Department of Health provides BCG vaccine for free in return for statistics on coverage of BCG vaccination. Currently, the neonatal BCG vaccination coverage rate in Hong Kong is over 99 % (Department of Health 2013). Local BCG revaccination programs for primary school children in Hong Kong have been stopped since September 2000 in view of the lack of evidence for additional protection from BCG boosters (Dantas et al. 2006; Karonga Prevention Trial Group 1996; Leung et al. 2001; Rodrigues et al. 2005; Sepulveda et al. 1992; Springett and Sutherland 1994; Tala-Heikkila et al. 1998). For residents below 15 years of age without previous BCG vaccination, direct BCG vaccination without prior tuberculin test is recommended.

4.2.5 Health Education

To increase public awareness of TB, which is important for passive case finding, health promotion messages in support of the TB control program are disseminated to the whole community as well as defined target groups through multiple channels.

Information about TB in Hong Kong is also disseminated through the internet (http://www.info.gov.hk/tb_chest). Professional guidelines on important aspects of TB are also available and updated regularly.

4.3 A Stagnated Decline in TB Notification in Recent Decades

After reaching a record high around 700 per 100,000 populations in 1952, the TB notification rate in Hong Kong declined significantly in the subsequent four decades (Department of Health 2013). Since the early 1990s, the decline has slowed down. Described as stagnation or a stagnated trend (WHO Western Pacific Regional Office 2002b), the phenomenon has also been noticed in neighboring countries with intermediate TB burden such as Singapore, Malaysia, Japan, and Brunei. The stagnated decline is probably attributable to a high burden of latent TB infection in the community interacting with several major factors, namely, aging of the TB epidemic, aging of the population, and miscellaneous lifestyle and socioeconomic factors.

4.3.1 Aging of the TB Epidemics

Aging of the epidemic refers to a decreasing proportion of active TB cases due to progressive primary infection and exogenous reinfection alongside an increasingly important contribution from endogenous reactivation. This phenomenon is most prominent when the risk of infection reaches a very low level below 10 per 100,000 population (WHO Western Pacific Regional Office 2002b). The discovery of effective TB drugs in the 1950s and the advent of the short-course chemotherapy in the 1970s have hastened the aging of the TB epidemic in countries with intermediate TB burden including Hong Kong. The larger the pool of infected individuals in the community, the greater is the contribution of TB cases due to endogenous reactivation. As the latency period for TB disease can be lifelong, the rate of endogenous reactivation will take many years to respond to control measures that are directed primarily at reducing transmission. A population-based molecular and conventional epidemiological study suggested that about one-fifth to one-quarter of the new TB cases in Hong Kong near the turn of the millennium were due to recent transmission (Chan-Yeung et al. 2006). Aging of the TB epidemic in Hong Kong has also been demonstrated by age-structured mathematical models (Vynnycky et al. 2008; Wu et al. 2010). An age-period-cohort model has also suggested that a stagnated decline will continue for a few decades after 1990 (Wu et al. 2008).

4.3.2 Aging of the Population

Compared with the average TB notification rate in the general population, the age- and sex-specific TB notification rate demonstrated a bimodal distribution with substantial increase after the age of 15, followed by gradual continuous increase after the age of 44 among males and the age of 59 among females (Department of Health 2013). The marked difference in the age-specific TB notification rate between the elderly and the general population may explain why the proportion of elderly in the TB patient population has increased out of proportion to the linear growth of the proportion of elderly in the general population over the last five decades (Leung and Tam 2011). In 1990, the proportion of elderly aged 65 years and above was 8.5 % in the general population and 21.2 % in the TB patient population. In 2010, corresponding proportions were 12.9 % and 40.4 % (Leung and Tam 2011). While the difference in age-specific TB notification rates may be largely attributed to a large pool of LTBI among the older cohorts, aging and the associated decline in host immunity probably contribute to the progression from infection to disease.

4.3.3 Lifestyle and Socioeconomic Factors

A number of local studies have examined the association between TB disease and smoking (Leung et al. 2003, 2004a, 2007, 2010). Smoking accounted for about 18.7 % of the TB risk and 45 % of the sex difference in TB risk of an elderly cohort in Hong Kong (Leung et al. 2004a). Passive smoking accounted for 13.7 % of active TB in a cohort of female elderly nonsmokers (Leung et al. 2010). Smoking increases the risk of both TB infection and subsequent development of disease among silicotic patients and may account for about one-third of active TB disease among silicotics (Leung et al. 2007).

The association between poverty and TB is more conflicting (Chan-Yeung et al. 2005; Leung et al. 2004b). Despite the virtual elimination of absolute poverty by a well-developed social assistance scheme in Hong Kong, low household income in the neighborhood was found to be significantly associated with TB (Pang et al. 2010).

Alongside an improvement in socioeconomic conditions, lifestyle change, and advancement in medical technology is an increase in the prevalence of comorbidities such as diabetes mellitus, end-stage renal failure, hematological and reticuloendothelial malignancy, and the use of immunosuppressive therapy for autoimmune diseases and posttransplant patients. These chronic conditions weaken the host immunity to a different extent, thereby increasing the risk of progression from infection to disease. A survey in 1999 showed that about one-quarter of all notified TB cases in Hong Kong had one or more comorbid conditions that increased the risk of TB disease (Leung and Tam 2002).

4.3.4 Current Minor Factors That May Adversely Affect TB Control in the Future

4.3.4.1 TB–HIV

In Hong Kong, TB and HIV health services are placed under the same branch of the Department of Health. The two services collaborate closely with each other in the combat of TB and HIV. All TB patients are offered an HIV test on a voluntary basis. Since 1996, a TB–HIV registry has been maintained by the Department of Health to monitor TB–HIV co-infected cases. Both pulmonary TB with CD4 counts below 200/μL and extrapulmonary TB at any CD4 count are AIDS-defining conditions in Hong Kong (Lee et al. 2007). From 2009 to 2011, TB ranked after *Pneumocystis jiroveci* pneumonia as the second most common primary AIDS-defining illness in Hong Kong (Department of Health 2013).

In line with a relatively low rate of HIV infection among various categorical groups in Hong Kong (Hong Kong Advisory Council on AIDS 2001), both unlinked anonymous screening from the early 1990s to late 2008 and voluntary HIV antibody testing from 2005 to 2011 have revealed HIV seropositive rates largely ≤ 1 % among TB patients (Department of Health 2013). The prevalence of MDR-TB among TB-HIV co-infected subjects reported to the TB–HIV registry between 1996 and 2011 is 1.1 %, which is comparable with that among culture-proven TB patients without HIV infection. No XDR-TB cases have been detected among reported TB–HIV cases (Department of Health 2013).

Thus, although the risk of progression from infection to disease is as high as 5–10 % per annum among the HIV co-infected (Jensen et al. 2005), HIV infection is unlikely to have a major impact on the TB epidemiology in Hong Kong in the foreseeable future.

4.3.4.2 Emergence of M/XDR-TB

Registries are in place to keep MDR-TB and XDR-TB under close surveillance. MDR-TB and XDR-TB constitute around 1 % and 0.1 % of culture-proven TB patients, respectively. Notwithstanding a low prevalence of MDR-TB, the global emergence of MDR- and XDR-TB and high rates of drug-resistant TB in neighboring areas have raised concerns in the control of TB, especially in view of an increasingly mobile population. New measures have thus been introduced to address these new challenges. The Prevention and Control of Disease Ordinance, substantially updated and revised from an older ordinance, was introduced in Hong Kong in 2008 to incorporate measures in compliance with the International Health Regulations (2005) promulgated by the WHO. Provisions that are operational in nature, such as measures to prevent cross-boundary spread of XDR-TB, are included in the regulation.

4.4 The Way Forward

The Stop TB Partnership's Global Plan to Stop TB 2006–2015 has set its target to halve TB prevalence and death rates by 2015 compared to the rates in 1990 (Stop TB Partnership 2006). The baseline TB notification and death rates in Hong Kong in 1990 were 114.1 and 6.7 per 100,000 population, respectively. Although Hong Kong achieved the millennium development goal regarding the TB death rate in 2010, when the crude death rate dropped to 2.7 per 100,000 population, the crude notification rate in 2010 (72.5 per 100,000 population) was still significantly higher than the corresponding millennium development goal (Department of Health 2013).

With the aging of the population, frequent population movement, and global resurgence of TB complicated by MDR-TB and XDR-TB, there is a continuing need to step up local TB control measures, promote community awareness and support, enhance multidisciplinary and international collaboration, and invest in research and development.

Collaborative efforts have been made in the development of new diagnostic tools, drugs, and drug regimens. New interferon-gamma release assays are being compared with the traditional tuberculin skin test in the targeted screening of latent TB infection among close TB contacts, silicosis patients, HIV-infected subjects, and other immunocompromised individuals including those under treatment with anti-TNF agents. Shorter regimens are required to facilitate the treatment of both LTBI and TB disease. Multicentered clinical trials are under way to explore new treatment-shortening regimens in different parts of the world. In line with the previous collaboration between the Hong Kong Chest Service and the British Medical Research Council in conducting TB trials of standard 6-month regimens, the Hong Kong TB Service joined the TB Trials Consortium in 2009 to evaluate new TB treatment regimens. It is hoped that some of these new tools and regimens in the pipeline will translate into effective, safe, and affordable tools that are suitable for large-scale implementation at the point of care.

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Chapter 5
Breakthrough Strategy for TB Control in Indonesia

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5.1 Background

5.1.1 National History and Current Status of Infectious Diseases in Indonesia

Indonesia is the largest archipelago in the world, with an estimated total of 17,504 islands distributed over more than 2000 km from north to south and 5000 km from east to west across the equator. The country is situated between two oceans, the Pacific and the Indian, and bridges two continents, Asia and Australia. There are five large islands (Sumatra, Kalimantan, Java, Sulawesi, and Papua) and two archipelagos (the Maluku and the Nusa Tenggara). The other islands are smaller and many are unpopulated. The island of Java counts for more than half of the Indonesian population (58.1 % in 2005). Administratively, there are 33 provinces, 399 districts, and 98 municipalities (BPS-Statistics 2012). Based on the 2010 census, the population reached 237,556,363 (50 % males, 27 % in the age group of 0–14 years, 68 %

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in the age group of 15–64 years, and 5 % over 65 years) with an annual growth rate of 1.35 % (BPS-Statistics 2010; MoH 2010). In 2010, 54.2 % of the country's population was urban.

The successes of national development over the last 5 years have been reflected in several important indicators. The Human Development Report revealed that the Indonesian Human Development Index increased from 0.71 in 2004 to 0.73 in 2007 (UNDP 2009). Agriculture is fundamental to Indonesia's economy. The Gross Domestic Product (GDP) per capita grew steadily from Indonesian Rubiah (IDR) 6.75 million in 2000 to IDR 30.81 million in 2011 (BPS-Statistics 2012).[1] This elevated Indonesia to one of the lower middle income countries in the global ranking. Accelerated economic growth has further contributed to a decline in poverty level, which has been reduced from 14.60 % in urban areas and 22.38 % in rural areas in 2000 to 9.23 % and 15.72 %, respectively, in 2011 (BPS-Statistics 2012).

There have been considerable improvements in the general health status of the population in the past decades. While there has been a significant decrease of maternal mortality ratio (MMR) in the last few years, Indonesia did not reach the Millennium Development Goals (MDGs) target MMR of 102 by 2015. Low access and quality of maternal health services remain the main causes of high maternal mortality, as shown by the low proportion of deliveries assisted by skilled birth attendants. Child health indicators, marked by infant mortality rate (IMR), under-five mortality rate, and neonatal mortality rate (age 0–28 days) all show a decline. The Demographic and Health Surveillance data revealed a decline of IMR from 35 to 34 per 1000 live births in 2007. Indonesia is estimated to have just reached the MDG target IMR of 23 per 1000 live births by 2015 (You et al. 2015).

Infectious disease, in addition to the increasing trend of noninfectious diseases, remains an important public health problem. According to recent estimates (WHO 2012), respiratory tract infections caused 10.3 % of total deaths for all ages in Indonesia in 2008, while other infectious and parasitic diseases contributed to 11.5 % of deaths in the same year, of which 35.9 % was due to tuberculosis (TB). The HIV epidemic in Indonesia is among the fastest growing in Asia (NAC 2010). There were 333,200 people living with HIV in Indonesia at the end of 2009. Asian Epidemic Modeling projects HIV prevalence among Indonesians aged 15–49 will increase from 0.22 % in 2008 to 0.37 % in 2014. Injection drug use and sexual transmission will continue to be the main modes of transmission within that period. The cumulative number of reported AIDS cases rose sharply from 2682 cases in 2004 to 19,973 in 2009. In 2004, only 16 out of 33 provinces had reported HIV cases but by the end of 2009, AIDS cases were reported in 32 of Indonesia's 33 provinces. Although most provinces are considered to have a concentrated epidemic, Papua province has one of the highest HIV prevalence rates at 2.4 % (BPS-Statistics and MoH 2006).

[1] USD was equivalent to IDR 9000 in 2012.

5.1.2 National Healthcare in Indonesia

Indonesia established a public health system using a design founded on primary healthcare concepts in the 1980s through its Health Sector Development Plan. The model focuses on extending basic health services to the poor and relies on providers with modest training; the providers operate at the periphery, but use a referral system. The Health Sector Development Plan made health services more accessible for most of the population, and health outcomes have improved consistently from the 1980s to the present. In 1999, the government of Indonesia initiated a process of decentralization, whereby districts became the key players in all fields of governmental activities, including healthcare.

In efforts to equally share the benefits of a rapidly growing economy, the government expanded its network of public health facilities under the principle of "Health for All," or universal access to basic care (Barber et al. 2007). In the mid-1980s, the Indonesian government began to expand a network of primary healthcare facilities based on population targets, with one community health center (also known as Pusat Kesehatan Masyarakat or Puskesmas) per 30,000 people and one auxiliary center for every 10,000 people. The system is supported by a referral system consisting of district, provincial, and central hospitals that provide secondary and tertiary care.

The number of general and specialized hospitals increased from 1145 units in 2000 to 1655 in 2010, bringing a ratio of 75 hospital beds per 100,000 population. The ratio of health centers to 100,000 population reached 3.6 (MoH 2010), and at present 94 % of the population have access to health facilities within 5 km or less of their home (NIHRD 2007). However, the population in the remote areas of Eastern Indonesia still faces barriers to access health facilities. Notably, 52 % of these hospitals are privately owned. The number of health workers in 2005 was 547,305 (250 per 100,000 population), with nurses being the majority (51.9 %). There were 40,963 general practitioners (18.7 per 100,000 population) and 11,765 specialist physicians (5.38 per 100,000 population) working in the country in 2005. Maintaining the network of health facilities described above has been challenging given resource constraints (Barber et al. 2007).

Indonesia is in transition in terms of epidemiological and demographic factors; it is also adjusting to the political and administrative decentralization of the health sector that was initiated in 1999. The total health expenditure as a percentage of GDP remains low, at 2.2 % in 2007 (WHO 2010), and due to the global economic crisis the health sector experienced several budget cuts. Facing pressure to keep health spending low, the Ministry of Health promoted an expansion of the private sector in the mid-1990s, encouraging those who were able to pay to self-select out of public facilities. The Indonesian healthcare services today represent a mix of public and private providers (Hidayat et al. 2004). Public providers include hospitals, health centers, and health subcenters. Private for-profit providers consist of private hospitals, private clinics, and private practitioners. Although these providers are generally available in urban areas, doctors in public health centers and public

hospitals can offer private services after office hours, and thus private practitioners can be found in most rural areas as well.

In 2004, the government implemented the Law on the National Social Insurance System to improve health system performance and cover 76 million of the poor and nearly poor. To this end, general government health expenditure increased from 4.1 % of total general government expenditure in 1995 to 5.3 % in 2006. Significant weaknesses in the efficiency and equity of the current health system remain and, if not taken seriously, could have negative effects on the cost and effectiveness of Universal Coverage policy.

5.1.3 National History and Current Status of TB

5.1.3.1 TB Epidemiology

Indonesia is one of the countries with the highest TB burden in the world. The estimated prevalence of all types of TB cases is 690,000 (WHO 2011), and the estimated incidence is 450,000 new cases per year. Among the Asian countries, Indonesia has one of the sharpest increases in the number of HIV patients. A total of 12 provinces have been declared as priority provinces for HIV intervention. It is estimated that there are 190,000 to 400,000 people living with HIV in the country. The estimated HIV prevalence among new TB cases is still relatively low, but slowly increasing (WHO 2011).

HIV infection among the general adult population nationally is estimated at 0.2 %, and HIV infection is characterized as a concentrated epidemic. However, the prevalence in Indonesia's Papua province is 2.5 %, which is considered a generalized epidemic. The proportion of Multidrug-resistant TB (MDR-TB) in 2010 is estimated to be around 1.8 % (range: 1.1–2.7 %) among new TB cases and 17 % (range: 8.1–26.0 %) among retreatment TB cases. Given the high burden of TB in Indonesia, this results in a total of around 6200 MDR-TB cases (5100 among new cases and 1100 among retreatment cases) in 2010 (WHO 2011).

5.1.3.2 The National TB Control Program (NTP)

Until 2010, implementation of the National TB Program in Indonesia fell under three different Directorates General (DGs) under the Ministry of Health: DG Medical Care, DG Community Health, and DG Disease Control and Environmental Health. The National TB Control Program operates under the Directorate of Communicable Disease Control, DG Disease Control, and Environmental Health. It provides surveillance and normative functions but has no direct responsibility for clinical activities. Health centers operate under the Directorate of Community Services, DG Community Health. They provide core Directly Observed Treatment

Short Course (DOTS) services under the guidance of the National TB Control Program. Public hospitals and clinics, under the Directorate of Medical Services, DG Medical Care, also provide TB services, but are largely independent of the National TB Control Program and the health centers. Many private facilities, private practitioners, prisons, military, and corporate entities also provide TB services, often with no direct linkage to the National TB Control Program. The Ministry of Health has launched the Indonesian Stop TB Initiative to forge bonds between the various agencies in Indonesia and the National TB Control Program to jointly address the challenges to reaching the targets for TB control.

In late 2010, the Ministry of Health was restructured and Medical Care and Community Health were brought together under one Directorate General. The TB services were fully integrated into the existing national health services where the district health office is the basic management unit of TB control. Community Health Centers (Puskesmas) are the pillars of TB control in every district. These health centers have been classified into three categories based on diagnostic function: (a) microscopy health centers—perform smear diagnosis for a group of satellite health centers; (b) satellite health centers—prepare sputum samples transported to the microscopy health centers for diagnostic examination; and (c) independent health centers—perform smear diagnosis with no linkage to satellite health centers. Currently, nationwide there is a total of 1649 microscopy health centers, 4140 satellite health centers, and 1623 independent health centers.

DOTS is generally carried out by family members supervised by health center staff. If patients miss an appointment, defaulter tracing is carried out through home visits. The district health office appoints a district TB supervisor who is responsible for surveillance (supervision, updating the treatment register, quarterly reporting), communication between the various facilities, and TB drug supplies. To perform these functions, the district TB supervisor regularly visits all DOTS facilities in the district. Large districts with many facilities commonly have more than one supervisor. At the provincial level, a core DOTS team is established, consisting of a Provincial Project Officer, a Provincial Training Coordinator, and a Provincial Technical Officer. The provincial DOTS team provides technical and managerial support to district TB control programs in addition to performing monitoring and training functions.

Government hospitals and associated clinics, under the Directorate of Medical Services, are providing a substantial amount of TB care, though a considerable number of them are not yet following DOTS guidelines. These hospitals are increasingly being linked with the NTP DOTS program. Private facilities and private practitioners are independent. Healthcare, including care for TB, is provided by prisons' medical service, the military, and corporate entities with increasing collaboration with the NTP. The coordination of NTP and collaboration between and within the various Directors General is of continuous importance for the seamless operation of the TB program. In 2009, almost 96 % of the over 8764 Health Centers had DOTS facilities, with 60 % and 25 % of the public and private hospitals, respectively, offering DOTS services (Table 5.1).

Table 5.1 Healthcare facilities providing DOTS in Indonesia

Type of facility	Total	DOTS
Health Center	8764	8376 (95.6 %)
Chest Clinic	28	28 (100.0 %)
Lung Hospital	9	9 (100.0 %)
Hospital	1655	666 (40.2 %)
– Public Hospital	539	321 (59.5 %)
– Parastatal Hospital	61	20 (32.7 %)
– Military-Police Hospital	155	73 (47.1 %)
– Private Hospital	863	217 (25.1 %)
Total	10,456	9079

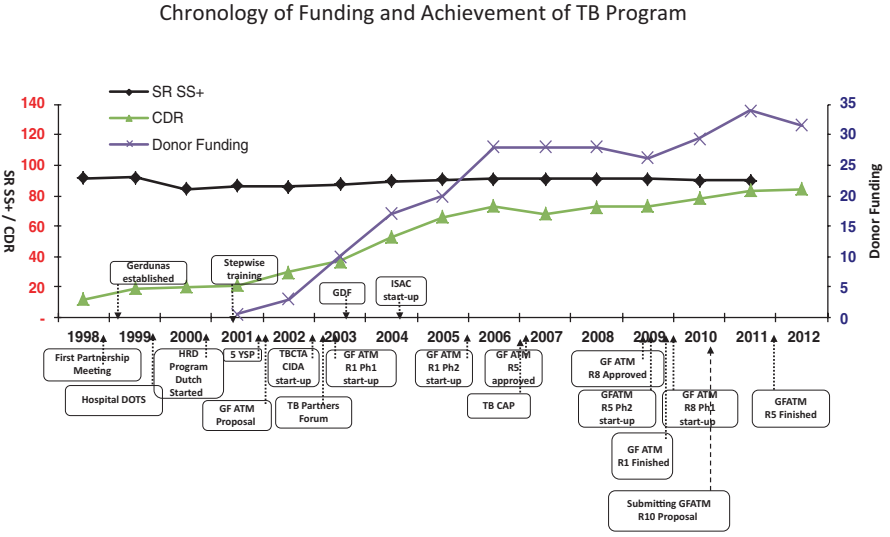

Fig. 5.1 Technical and financial assistance supporting Indonesia's TB program acheivement

5.2 Effective Control Measures: Lessons and Successes

Indonesia has made remarkable progress in TB control over the last decade. Acceleration of DOTS implementation since 2002 enabled Indonesia to become the first country in South East Asia to achieve the WHO global targets in 2006. In 2009, Indonesia maintained this program achievement with a case detection rate (CDR) of 73 % and treatment success rate of 90 %. These achievements were greatly facilitated by the technical and financial assistance of various organizations (Fig. 5.1).

The TB case detection rate rapidly increased from 30 % in 2002 to 76 % in 2006. The treatment success rate has been above 85 % since the year 2000, and it reached 91 % in 2007. Indonesia was the first high TB burden country in the WHO South

East Asia region to achieve the global targets for case detection (70 %) and treatment success (85 %). The average treatment success rate over the last 5 years is approximately 90 %. The achievement of this global target is a milestone in the national TB control program. Tuberculin surveys, used to estimate the annual risk of TB infection in school children, reveal a decline in annual risk of infection from over 3 % (in the period between 1972 and 1987) to rates varying between 0.9 % and 1.4 % in surveys conducted in 2007–2008 (Bachtiar et al. 2008, 2009).

The proportion of relapse and treatment failure still remains below 2 %, indicating that, in general, the rate of TB drug resistance among patients treated at healthcare facilities is still low. However, this data is mostly derived from Community Health Centers that have been implementing the DOTS strategy over the last 15 years. The problem of drug resistance is probably higher in the hospital and private sectors which have not been fully engaged in the TB control program. As a result, noncompliance to the DOTS strategy and the proportion of treatment dropout is higher in hospitals than in Puskesmas. Unknown numbers of TB patients are inadequately diagnosed and improperly treated by hospitals and private sector providers that are not reported to the NTP. High defaulter rate and irrational use of second-line drugs in hospitals and private sector are contributing to the increase of MDR/XDR-TB.

Out of the existing 485 districts in Indonesia, 138 are considered to be disadvantaged and called underserved districts. These districts are mostly in remote areas and have been designated as priority areas for accelerated development. Most of the population in Papua (>42 %) and West Papua (27–41 %) are still not fully covered by the national DOTS program. Indonesia also has more than 11 million urban poor facing major obstacles to access healthcare. Even health services for the poor cannot be accessed due to their unregistered status. According to NTP data from 105 prisons engaged in TB control services, 1865 inmates have been notified, of which 324 were smear positive. During the same period, TB contributed to 15 % of all deaths in the prisons.

Allocation of government funding for TB control is gradually increasing. In 2009, the total government budget for the operation of a TB control program was IDR 145 billion (16 million USD). This is a 7.1 % increase over the IDR 135 billion budget of 2008. Despite such increase, the government only contributed 23.4 % of the total national budget (IDR 621.5 billion or 70 million USD) required for TB control. International funding was used to meet the financial gap, which reached IDR 269.36 billion in 2009 or a 45 % increase from the previous year. Budget escalation for the TB control program in Indonesia was triggered by a strong motivation to accelerate the achievement of Millennium Development Goals. Despite a large amount of funding obtained from the central and local government as well as increasing support from international funding, the funding gap remains.

Closing the financial gap is critical. In particular, allocations from local government (province and district/municipality) to TB control are still far below expectations. Dealing with the weaknesses in financial mechanisms and endorsement of a resource allocation policy are crucial to ensure sustainability of the TB control program. Moreover, building of central and local partnerships is important to ensure

collaboration and communication among all sectors. It is expected that local economic growth of 6–7 % and local commitment to achieve target indicators of MDGs in 2015 will result in further closing of the current gap in the financing of TB control, halving it from 31 % in 2010 to around 15 % in 2014. If sufficient funding for TB remains available and a sustainable TB program is well managed, it can be realistically assumed that Indonesia will have achieved the 2015 MDGs targets for TB, as outlined in the third strategic plan (2010–2014).

The structure of Indonesia's public health system, based on the Puskesmas, significantly facilitated DOTS delivery of TB treatment at the community level. The country's human resource development plan and comprehensive training management structure proved to be a critical foundation for the rapid expansion of DOTS. This firm foundation made it possible to rapidly expand DOTS when the financing from external funding sources increased substantially in 2003. Donor financing, particularly that provided by The Global Fund and USAID, has been critical to the scale-up of TB control. This has boosted the rapid increase in case notification, which has quadrupled in 5 years. Lessons learnt from the temporary restriction of a grant from The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund) in 2007 revealed the vulnerability of the program: many well trained and experienced contracted staff at central and provincial levels resigned and activities slowed down. Consequently, there was some decline in TB notification and case detection rates, although treatment outcomes remained stable. Most importantly, the restriction highlighted the danger of donor dependence and, ultimately, the need for sustainable funding. Nevertheless, the inadequacies in financial management were successfully addressed.

5.3 Future Risks and Scenarios

Some important challenges need to be addressed to successfully achieve the MDGs. One of the main priorities is to strengthen the foundation of the human resource capacity in several technical areas such as the introduction of new diagnostic technologies, laboratory quality assurance, management of MDR-TB, and roll out of TB/HIV collaboration. Further expansion of private sector and hospital engagement, and improvement in the quality of care provided, are required for improved case detection and management and avoiding further creation of drug resistance. The existing drug and supply management system for both first-line and second-line drugs is still not functioning optimally. This poses a threat to the future drug supply if not addressed at all levels.

The NTP has been proactive in developing strategies to address many issues that impede TB control. However, continued financial and technical support is required to achieve these ends, as will maintain strong partnerships. The NTP's heavy dependence on donor funds must be addressed by increasing financial contribution at the district level. Sustainable funding, particularly at the district level, may be the most

critical factor in determining further expansion and long-term success of the NTP. If the program and the national government remain coordinated and committed, there is a strong possibility that the program will succeed.

5.4 Urgent Needs and Action Steps

If sufficient funding for TB remains available and all technical and managerial challenges are addressed properly, it can be realistically assumed that by 2015, Indonesia will have achieved the MDGs targets for TB. However, since 2007 a clear slowdown in acceleration of case detection is visible. This indicates the need to adjust current strategies in order to reach the "unreached," while at the same time maintaining the quality of current DOTS services. The strategies to address current bottlenecks and other challenges are described in the new national strategy for TB control 2011–2014 (MoH 2011). The major challenges are outlined below.

Limited access to quality DOTS services remains a major problem among the poor, urban slums, prisoners, those who live in remote border areas and islands, and specifically populations in Eastern Indonesia. Poor people living in the cities face mostly socioeconomic problems with access to DOTS. Most prisons are not yet integrated into the national TB program; thus, prisoners do not have equal access to DOTS services, yet the threat of TB/HIV and MDR-TB in these settings is real. TB infection control is also not in place in those prisons. Epidemiologic and surveillance data show that TB burden is higher in Eastern Indonesia. This region requires special attention, particularly in remote areas and, in particular, Papua province, due to the generalized HIV/AIDS epidemic. In addition, the gap in quality and quantity of human resources in this province is large, and thus it requires extra investment to meet the needs. Other challenges include the high number of dropout cases due to limited access, high cost of transportation, and opportunity costs due to geographic conditions.

Quality of TB case management in hospitals and private practices varies widely and is often not in line with national DOTS standards and International Standards for Tuberculosis Care (ISTC). These settings are characterized by high dropout rates. Internal and external networks for management of TB cases are often weak, including surveillance, monitoring, and supervision. Moreover, ISTC are not implemented as the standard for TB case management in these settings. ISTC are not yet adequately integrated in the medical curricula for most medical doctors, nurses, and midwives, nor are they included in the standards for accreditation and certification of the healthcare facilities. Despite great improvements, the networking among private practitioners, health centers, and hospitals is still weak. This includes the referral system between the various providers and government health services.

Coordination and collaboration between government and NGOs at the local level is still limited. Knowledge about TB and TB treatment is generally poor, and stronger interventions are needed for effective counseling and patient education.

Informing the rights and obligations of TB patients, as stated in a TB patient charter, through engagement of patient and community organizations is another main priority. Facilitation and social economic empowerment for TB patients are part of the efforts to meet these needs. All these efforts should be closely monitored and evaluated under clear regulations to ensure their continuity.

The theme for the National Strategy for TB control in Indonesia 2011–2014 is "Breakthrough toward Universal Access." Seven strategies have been formulated to achieve "a TB free, healthy, just, and self-reliant society."

1. Scaling up and improving quality DOTS service
2. Addressing TB/HIV, MDR-TB, and the needs of poor and other vulnerable groups
3. Engaging all public and private providers in implementation of International Standards for TB Care
4. Empowering TB patients and communities

supported by:

5. Strengthening the health system, including health research and development and TB control program management
6. Increasing commitment of central and local government
7. Enhancing research, development, and utilization of strategic information

The third strategy "Engaging all public and private providers in implementation of International Standards for TB Care (ISTC)" is implemented through a Public-Private Mix (PPM)-TB initiative to involve diverse care providers. NTP has made major efforts in the past to expand the link to the public and private hospital sectors. Hospital DOTS Linkage (HDL) Guidelines have been developed, and ISTC have been introduced and endorsed by all professional associations under the Indonesian Medical Association since 2006. Training material for HDL that includes ISTC has been developed and is now being used in an accelerated training program supported by The Global Fund. Additional technical surveillance officers have been employed by USAID/TBCAP (Tuberculosis Control Assistance Program), posted in strategic hospitals to monitor and guide the expansion of the hospital DOTS. ISTC Task Forces have been established in 32 out of 33 provinces. The progress in HDL is obvious; most hospital management show a strong commitment to join the DOTS strategy, however, the progress of implementation is slower than expected. So far around 400 general hospitals are regularly reporting to the NTP. However, HDL expansion is still hampered by lack of support from the majority of health professionals, in particular specialists rejecting DOTS for a variety of reasons. Despite recent evidence of high consumption of TB drugs in the private sector (Wells et al. 2011), the implementation of DOTS strategy among private practitioners so far has been insignificant.

There is a clear and imminent need for a conceptual breakthrough for scaling up PPM in Indonesia.

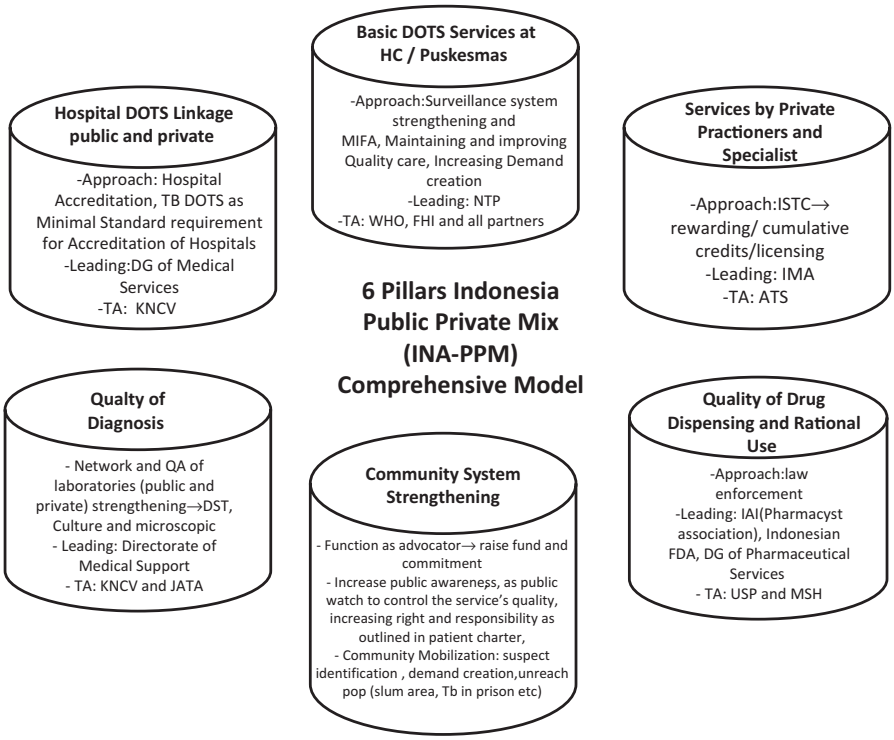

Fig. 5.2 The six pillars of Indonesia Public Private Mix Comprehensive Model

5.5 Conceptualizing the Breakthrough Strategy

The proposed breakthrough strategy for TB control in Indonesia is the Indonesian PPM (INA-PPM) model, which consists of six key components (Fig. 5.2). The first component involves strengthening the backbone of the DOTS strategy by maintaining and improving basic DOTS in the primary health centers. The second element comprises expanding HDL coverage utilizing the hospital accreditation scheme to standardize TB services in hospitals with technical support from TBCARE/Royal Netherlands Tuberculosis Association (KNCV). The third component concerns engagement of private practitioners through initiatives led by the Indonesian Medical Association with technical assistance from the American Thoracic Society (ATS). The fourth component minimizes irrational use of TB drugs through engagement of pharmacies with the support of the Indonesian Association of Pharmacists, the Food and Drug Administration, and DG Pharmaceutical with technical assistance from TBCARE/Management Sciences for Health (MSH) and United States Pharmacopeia (USP). The fifth component ensures high-quality diagnosis by strengthening laboratory capacity in collaboration with the Directorate of Medical

support and services with technical assistance from KNCV and Japan Anti-Tuberculosis Association (JATA) through TBCARE.

The sixth component completes the model by ensuring demand for the preceding five components through: (1) strengthening community mobilization; (2) enhancing local organization capacity; and (3) increasing advocacy. Strengthening community mobilization encompasses raising community awareness and knowledge on TB as well as promoting adequate health-seeking behavior change. Enhancing local organization capacity involves boosting technical and management capacities as well as nurturing a platform for networking. Advocacy strengthening concerns the enabling of local organizations to systematically encourage all care providers to provide services in accordance to ISTC and ensure their awareness of the patient's right to quality services. Ultimately, the sixth component is expected to empower community and increase demand for quality TB services.

5.6 Summary

The National TB Control Program achieved remarkable progress in controlling TB in Indonesia; however, progress has decelerated recently as new challenges have emerged. Major challenges include the large number of TB cases remaining unnotified to NTP and non-NTP providers prescribing TB treatment not in accordance with the DOTS strategy. Hence, optimum leverage can be achieved by effectively engaging diverse care providers to implement DOTS. We believe that the INA-PPM model, with its six components, can effectively guide operational interventions to break through persistent barriers for TB control in Indonesia and prevent further emergence of TB drug resistance.

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Chapter 6
TB Control in Nigeria

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6.1 Introduction

Nigeria, located in West Africa, is the most populous African nation with an estimated population of 170 million in 2012. Nigeria has three tiers of government: Federal, 36 States plus the Federal Capital Territory, and 774 Local Government Areas (LGAs). The National Council on Health (NCH) is the highest decision and policy-making body on health. The national health system is structured to provide healthcare services along the three tiers of government at the following levels—primary (primary/comprehensive health centers), secondary (district/general hospitals), and tertiary (specialist/teaching hospitals) institutions. The national policy on Public–Private Partnership, developed in 2005, highlights the features that will ensure both sectors to complement each other in achieving national health sector objectives. The major sources of finance for the health sector in the country are the three tiers of government, the health insurance institutions (private and public), the private sector (firms and households), donors, and mutual health organizations (National Population Commission of Nigeria 1991; Lucas 2006, 2007).

In 2000, the Nigerian health system performance was ranked 187th among the 191 member states of the World Health Organization (WHO) (Federal Ministry of

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Health 2007). The health trends and indicators were unsatisfactory, coupled with challenges of the Federal Ministry of Health (FMOH) to monitor the implementation of all its policies and guidelines at all levels. The national health system reflects a lack of clarity or consensus on the roles and responsibilities of the three individual tiers. With the present parallel funding arrangements for some programs, the implementation of joint planning and management mechanisms is necessary to achieve the desired health sector objectives (Lucas 2006, 2007).

6.2 Healthcare Financing in Nigeria

The public sector in Nigeria is financed through the federation account's general revenue, which is allocated to the various levels of government based on an agreed formula. Revenue sources include royalties and fees from the oil sector, general tax revenue including sales and value-added taxes, social health insurance, and cost recovery including user fees in some public health facilities (Federal Ministry of Health 2007). The WHO database estimates that the public sector spending on healthcare accounts for 3.5 % of the total government expenditure, which is the lowest in Africa apart from Burundi. This is extremely low in context of the commitment by African heads of state to devote 15 % of government funds to the health sector. Out-of-pocket payments account for about 63 % of healthcare financing—one of the highest proportions in Africa. In addition to the federal financing mechanisms, bilateral and multilateral donors also play a vital role in financing healthcare in Nigeria (Federal Ministry of Health 2007). Financing by the office of the Senior Special Assistant to the President on Millennium Development Goals (MDGs), which is from the proceeds of debt relief, is also regarded as a donor financing mechanism. Many healthcare interventions have been implemented through this fund. However, the sustainability of donor financing is a serious concern in this era of a global economic meltdown (Lucas 2006).

6.2.1 Tuberculosis Program Financing

The tuberculosis (TB) program enjoys financial support from the different tiers of government. This support varies among the States and LGAs with some receiving support only from the FMOH and development partners. There was an increased financial commitment from the FMOH regular budget in recent years (2006–2009), with the exception of 2010, when support came from MDG grants only.

Nigeria is one of the countries granted funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund). Nigeria's TB program received a grant of $25,570,067 in Round 5 (implemented from January 2007 through December 2008) and $60,264,444 in Round 9 (implemented from July 2010 through December 2012). Other sources of funding include the USAID/TBCAP (over $4 million for 2007–2009) and CIDA grant of $876,809 in 2007. There are many

other partners supporting the TB program at different levels, especially on the implementation of TB/HIV activities (Federal Ministry of Health 2010a). There are three major challenges involved in this financing. First, not all budgeted funds are released. For example, only 58 % of the total budget of FMOH was released in 2010, while funds for TB varied from 0 to 10 % of the regular budget (Federal Ministry of Health 2010b). Second, there is no centralized database of the financial contributions of all tiers of government and partners at the central unit of TB control. Third, most funds are for routine activities with little or no budget line items for research.

6.3 Nigerian Healthcare Indicators

The major sources of data on health indicators are the FMOH, the National Population Commission, the Federal Office of Statistics, the National Agency for the Control of AIDS, the WHO Country office, and other international institutions. Data quality varies between sources.

Indicator	Estimate
Population	144 million (2006)
Gross national income per capita (US$)	300 (2002)
Gross Domestic Product (GDP) per head (US$)	1600 (2010)
Under-five mortality rate per 1000 live births	201 (2002)
Incidence of TB per 100,000 people (WHO 2009)	311 (2007)
Prevalence of HIV infection (Federal Ministry of Health 2008a)	4.6 % (2008)
Average life expectancy at birth (years, 2002)	
Male	45
Female	46

Source: World Development Indicators. Washington, DC: World Bank, 2004 (Updated from Adeyi et al. 2006)

6.4 National TB Control Program in Nigeria

6.4.1 Introduction

Nigeria is the only West African country among the 22 High Burden Countries (HBC) with TB; it ranks fourth overall and first in Africa. In 2007, the WHO estimated an incidence rate for all forms of TB to be 311 per 100,000 people. The incidence of smear-positive cases annually is 131 per 100,000 people and a prevalence of 546 per 100,000 people (WHO 2009). Other African countries among the 22 HBC are the Democratic Republic of Congo, Ethiopia, Kenya, Mozambique, South Africa, Uganda, Tanzania, and Zimbabwe. All the African countries have similar challenges

with the HIV epidemic, a weak healthcare system, a human resource crisis for healthcare, and very weak peripheral laboratories. Other concerns facing the region are a low capacity for multidrug-resistant tuberculosis (MDR-TB) programs, a weak logistic management system, and a slow pace of scaling up Public Private Mix (PPM) and community TB care (WHO 2006). The prevalence of HIV among TB patients increased from 2.2 % in 1991 to 19.1 % in 2001 and has grown to an estimated 27 % at present although higher levels have also been observed.

6.4.2 History of the Nigerian TB Program

TB control activities before the establishment of the National TB & Leprosy Control Program (NTBLCP) in 1989 were mainly in a few secondary, tertiary, and faith-based health facilities. TB care was more synonymous with the missionary hospital than government health facilities. In that era, TB cases were managed based on individual cases. There were no national guidelines or policies on diagnostic criteria, drug combinations, dosages, or duration of treatment. Patients were not systematically followed up, and therefore there was no evaluation of outcome of care. This early era also lacked a comprehensive monitoring and evaluation (M&E) system. Therefore, the actual burden of TB during this period is not clear.

NTBLCP was established in 1989 and officially launched in February 1991 with a mandate to coordinate TB and leprosy control activities in all states in Nigeria in order to significantly reduce the public burden of the two diseases. The program is structured along the three tiers of federal, state, and local governments. The NTBLCP has the overall responsibility for the development of policy and operational guidelines, resource mobilization, procurement, and management of all commodities. The NTBLCP also coordinated the implementation of the TB services at the state levels and among partners. NTBLCP has a comprehensive M&E system that links services at all levels.

State TB programs are run by the TB & Leprosy Control Officer (TBLCO) under the department of public health or primary healthcare. The TBLCO is responsible for program planning, implementation, supervision, and M&E of the program.

At the LGA level, all health facilities providing TB services are coordinated and supported by the TB & Leprosy Supervisor (TBLS). The TBLSs monitor all TBL activities at the facility level, collect data, analyze, and report to the TBLCO on a quarterly basis on the performance of the program at the LGA level (Federal Ministry of Health-Nigeria and National Tuberculosis and Leprosy Control 2010c).

The TB services are structurally integrated within the health facility with designated and trained officers. Some facilities diagnose and treat patients; others can only offer treatment. Some TB trained staff are equally trained to offer HIV counseling and testing and to link patients to HIV/AIDS care services.

The NTBLCP adapted DOTS strategies in 1993 and developed a series of guidelines including standard recording and reporting tools, an M&E system, and the current (5th) edition of the “workers manual” which was revised in line with the

expected task of general healthcare workers at all levels of care. The manual covers all areas of the Stop TB strategy. The program developed two strategic plans (for 2001–2005 and for 2006–2010) (Federal Ministry of Health-Nigeria and National Tuberculosis and Leprosy Control 2007).

6.4.3 TB Control Activities in the Era of USAID/CIDA, The Global Fund, and Government Funding

The program implementation after adapting DOTS strategy was very slow, as only 14 of the 36 states had the complete support of the German Leprosy & TB Relief Organization and four other states had partial support from the Netherlands Leprosy Relief for the implementation of TB services. In 2002, DOTS centers covered 22 % (1605/6089) and microscopy centers covered 23 % (417/1903) of their targeted populations.

With the support of a USAID/CIDA grant, TB services were expanded to an additional 17 states in the country and all states were given DOTS coverage. The number of DOTS centers increased from 1605 in 2002 to 2015 centers in 2005 and microscopy centers increased from 417 in 2002 to 547 in 2005. The support included supplies of all TB commodities, laboratory microscopes, and capacity development of general healthcare workers. In 2006 reports, the 17 USAID/CIDA supported states contributed 50.6 % of all cases registered and 51 % of smear-positive cases nationwide. Figure 6.1 shows the trend over a period of 5 years (2001–2006) (Kabir et al. 2010; Federal Ministry of Health-Nigeria and National Tuberculosis and Leprosy Control 2010a).

The USAID/CIDA grant was supported in 2007 by the first phase of The Global Fund Round 5 (a gap filling fund) based on the strategic plan. Other funding sources were TB CAP and USAID funding for TB/HIV collaborative activities. Figures 6.2 and 6.3 depict the trend of events over time in the Nigerian TB program.

The DOTS coverage by LGAs was 100 % by the end of 2008, and by the end of 2009, the DOTS and microscopy coverage by population was 57 % and 54 %, respectively (Federal Ministry of Health-Nigeria and National Tuberculosis and Leprosy Control 2010b).

6.4.4 TB Control Performance Indicators

The case detection rate has persistently remained low in Nigeria, at 28.9 % in 2009, while the case notification rate for all cases of TB increased from 23.9/100,000 people in 2002 to 56.5/100,000 people in 2009. The treatment success rate has remained above 80 % in the last years, with a drop in failure rate from its peak of 11 % in 2006 to 2 % in 2009 (Federal Ministry of Health-Nigeria and National Tuberculosis and Leprosy Control 2007). See Fig. 6.4.

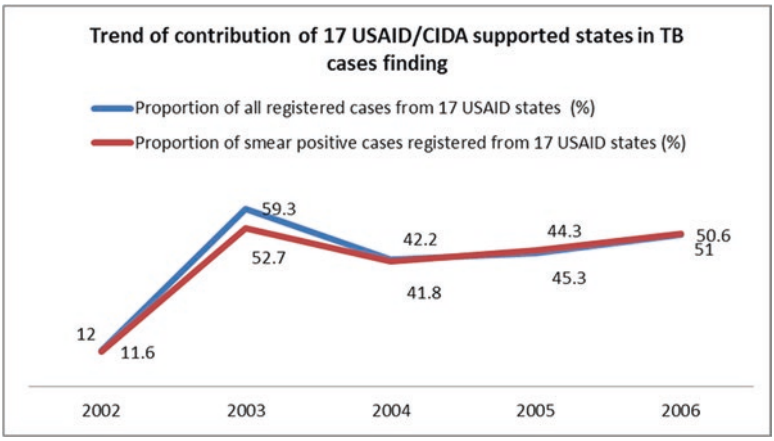
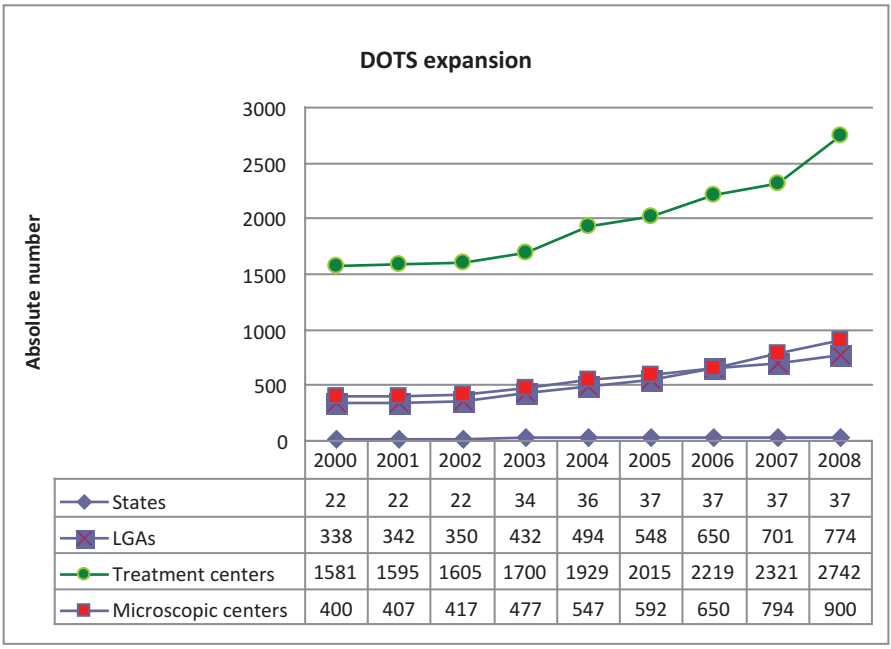


Fig. 6.1 Five year trend (2002–2006) of TB case notification rate in 17 USAID/CIDA supported States in Nigeria



	2000	2001	2002	2003	2004	2005	2006	2007	2008
States	22	22	22	34	36	37	37	37	37
LGAs	338	342	350	432	494	548	650	701	774
Treatment centers	1581	1595	1605	1700	1929	2015	2219	2321	2742
Microscopic centers	400	407	417	477	547	592	650	794	900

Fig. 6.2 Nine year trend (2000–2008) of service delivery (DOTS & microscopy) expansion by states and LGAs

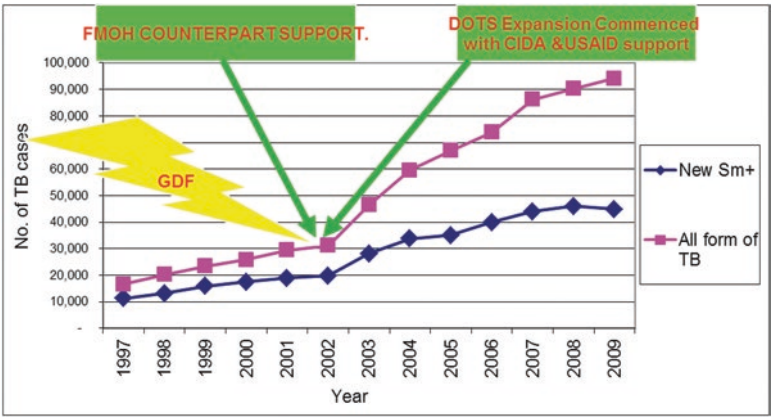


Fig. 6.3 National trend of number of TB cases notified for period 1997–2009

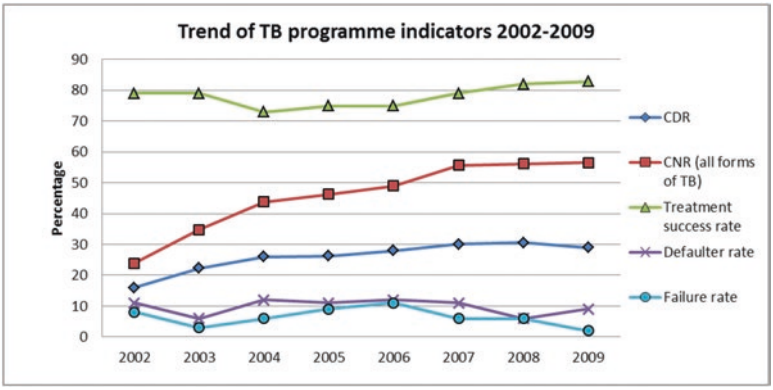


Fig. 6.4 National trend of TB key indicators (2002–2009)

6.4.5 TB/HIV Indicators

Even though TB/HIV collaborative activities are one of the Stop TB strategies, implementation especially at the facility level has a lot of challenges, most of which are related to the vertical nature of each program operating within health facilities with support from different partners. The prevalence of HIV among TB patients increased from 2.2 % in 1991 to 19.1 % in 2001, to an estimated 27 % at present, although higher levels have also been observed.

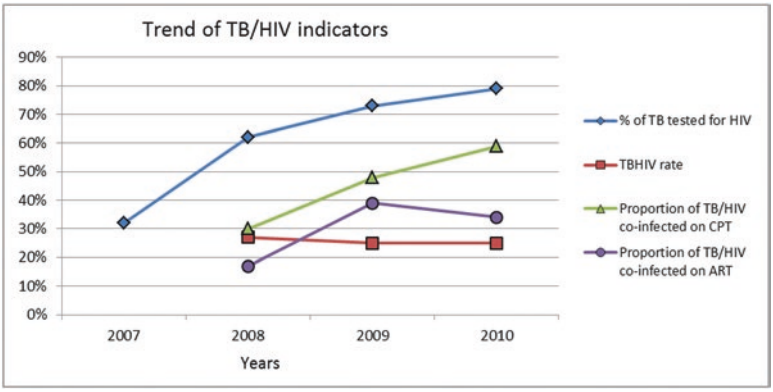


Fig. 6.5 Four years trend of TB/HIV indicators. Source: NTBLCP report 2010

The last 3 years recorded some progress, especially on the uptake of HIV counseling and testing among TB patients, with 79 % of TB patients screened for HIV in 2009. The co-infection rate steadily increased from 2.2 % in 1991 to 25 % in 2010. The proportion of TB/HIV co-infected on co-trimoxazole preventive therapy (CPT) increased from 30 % in 2008 to 59 % in 2010, while the proportion on Anti-Retroviral Therapy (ART) was about 34 %. Use of ART among the co-infected patients is low because of the disproportionate distribution of ART and DOTS centers: there are less than 500 ART sites compared to 3459 DOTS centers (Federal Ministry of Health-Nigeria and National Tuberculosis and Leprosy Control 2007; Federal Ministry of Health-Nigeria and National Tuberculosis and Leprosy Control 2010b) (Fig. 6.5).

6.4.6 MDR-TB

Drug-resistant (DR) TB was first reported in Nigeria in the 1970s, when resistance to either isoniazid or streptomycin was found in 7 % and 2 % of isolates, respectively, from Zaria in the north of the country (Idigbe et al. 1992). Subsequently, individual resistance to isoniazid (38 %) or rifampicin (2 %) was found in isolates from Lagos (Lawson et al. 2010). The WHO estimates lower burdens of MDR-TB in the country; recent studies reported prevalence of 4 %, 12.5 %, and 16 % from unselected groups of naïve and retreatment TB patients in Calabar, Abuja, and Jos in central Nigeria (Ani et al. 2009; Otu et al. 2013a, b; Habib 2009). The main challenge to MDR-TB care in Nigeria has been access to early diagnosis and treatment. As of the end of 2010, only three facilities (two public and one private) offered TB culture and drug susceptibility testing. There is only one treatment site. Although the challenges and specter of MDR-TB in HIV infections have been acknowledged (Idigbe et al. 1998), small-scale studies have not yet confirmed such associations in Nigeria (Ani et al. 2009; Gidado and Ejembi 2009).

6.5 Key Lessons Learned in the Implementation of the Stop TB Strategy

1. A TB program should strive to apply guidelines and ideas within the context of its location. Implementation of a universally identical program may not be appropriate or feasible. For example, programs for Community TB Care in an East African country or Community MDR-TB care in Lesotho may not be successful in Nigeria if copied directly without adaptation.
2. DOTS program expansion by population is not equal to DOTS program access. Many of the states in Nigeria have at least 50 % DOTS coverage by population, but when compared to DOTS coverage by health facilities, most states have less than 15 % of the total health facilities covered by DOTS services (Federal Ministry of Health-Nigeria and National Tuberculosis and Leprosy Control 2010a). See Fig. 6.6 for an analysis of the North West Zone in Nigeria.
3. DOTS and acid-fast bacilli microscopy trainings are not synonymous to DOTS expansion, as DOTS expansion implies the ability of a facility to detect and treat cases. Therefore, before training activities are conducted, facilities need to be selected and provided with the required tools for TB services such as drugs, microscopes, lab supplies, and recording and reporting forms. At the moment, there is a lag period of over 6 months between training activities and the commencement of TB services in many of the states, and the number of trainings is not commensurable to case detection.
4. Most TB patients are currently detected from secondary and tertiary health facilities (some states report over 50 % contributions from them), while the DOTS expansion program was basically primary healthcare based. If TB

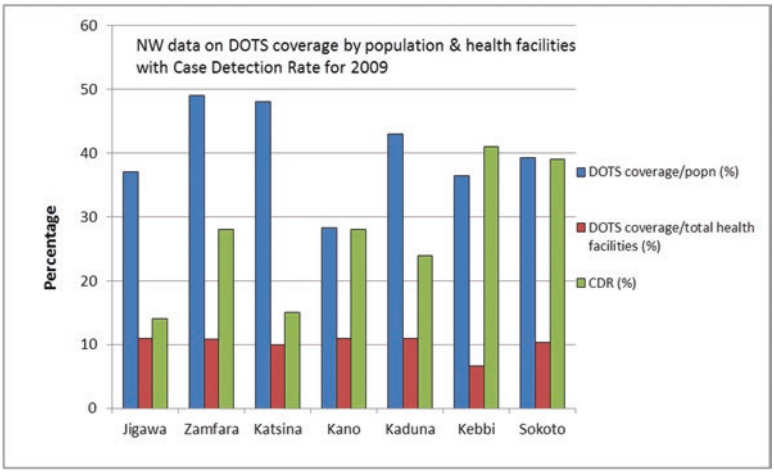


Fig. 6.6 Comparison of DOTS coverage by population and Healthcare facilities with case detection rate by states in Northwest Nigeria

targets have to be achieved, peripheral laboratories and Primary Health Centers must be functional.

5. Resources for TB control are not the main challenge but coordination of partners and aligning their activities to a strategic plan, such as the concept of "3 Ones": one authority (NTBLCP), one strategic plan, and one M&E plan.
6. Technical knowledge on TB alone is not sufficient for TB program managers. Knowledge and skills on leadership, management, and advocacy is necessary as well.
7. Most patients utilize the private sector; therefore, TB services should scale up PPM DOTS in all major cities of Nigeria. Where PPM is practiced, there is better case finding and treatment outcome among the private care providers (Federal Ministry of Health 2008b).
8. The Advocacy Communication Social Mobilization (ACSM) is still not bringing the desired results despite generous funding (22 % of the current Global Fund Round 9). This is likely due to poor strategy, where the wrong media channels are used for the wrong target groups at the wrong time, leading to serious gaps between available services and utilization.
9. The use of hospital DOTS community has improved access for TB services by other departments in some facilities while reducing defaulter rates, as the committee coordinates patient management and discharge.
10. Ensuring all TB service providers can at least offer counseling and testing for HIV with effective referral has improved the proportion of TB patients who know their HIV status.
11. The use of a TB clinical screening tool at an ART clinic among all People Living with HIV (PLHIV) has improved case detection for TB among PLHIV.
12. Joint supervisory visits by the program staff and partners has reduced the burden on healthcare workers who receive frequent supervision without sufficient time to implement the recommendations.

6.6 Challenges for Implementation of Stop TB Strategy

General:

1. Public health facilities are still weak, especially primary healthcare, with low utilization.
2. There are frequent strikes by different cadres of health professionals in public service.
3. Health personnel distribution is grossly uneven between urban and rural areas and between primary, secondary, and tertiary health facilities.
4. Vertical programs should be avoided and there should be better coordination and streamlining between health programs (e.g., Malaria, TB, and HIV).
5. Health system strengthening is a very nice slogan but it is difficult to apply because of differing funding partners, policies, and priorities.

Program-specific goals based on the Stop TB strategy (WHO 2007; Federal Ministry of Health 2008b; Federal Ministry of Health-Nigeria and National Tuberculosis and Leprosy Control 2010b):

1. Ensure financial commitment by all tiers of the government for the TB program. At the moment, the TB program is highly dependent on donors with few states in Nigeria as exceptions.
2. Establish a database on financial contributions for TB services by all tiers of the government and ensure transparency and accountability among all stakeholders (government and partners).
3. Have states and LGAs take ownership of the TB program rather than seeing it as an NTBLCP program.
4. Strengthen peripheral laboratories including their infrastructure and staffing.
5. Improve access to quality diagnosis of TB among PLHIV, including improving access to TB culture for all symptomatic PLHIV who are smear negative.
6. Decentralize the logistics management system from NTBLCP to empower states and LGAs to take bigger responsibility in supervising and monitoring the appropriate use of commodities.
7. Harmonize and ensure the use of standard recording and reporting formats by all implementing partners.
8. Establish TB/HIV collaborative activities at the facility level with an effective referral system aimed to improve the uptake for HIV screening, CPT, and ART.
9. Provide an infrastructure for MDR-TB management including a laboratory network and treatment facilities.
10. Involve all professional and regulatory bodies with the aim of rapid scaling up of PPM, especially among private for profit providers.
11. Build capacity among NTBLCP staff on ACSM, especially for leadership, management, and lobbying skills.
12. Increase the number of civil society organizations with experience in TB, as the current number is inadequate.
13. Increase the strategic alliance between TB program and academia, especially in areas of research, as it is currently minimal.
14. Increase knowledge, skill, and time for research among the program staff.

6.7 Future Risk and Urgent Interventions Required

HIV infection is fueling TB resurgence and may potentially fuel drug-resistant TB. A co-epidemic in a populous country like Nigeria would have disastrous consequences. Although strides have been taken in providing care to HIV-infected patients, current ART and HIV care access is very far from meeting national demands because of funding shortfalls, manpower limitations, and poor coordination between service providers and policy makers. Given the challenges of clinical recognition, management, and prevention of TB in HIV infection, the major principles for control referred

to as the four "I"s should be implemented and widely scaled-up throughout the country. The four "I"s stand for: Intensive TB case finding and surveillance; Infection-control measures; Isoniazid Preventive Therapy (IPT) when appropriate; and Instituting ART and co-trimoxazole to all HIV-TB coinfected patients. Both ART and IPT independently confer protection against TB reactivation in HIV infection but their combined synergistic effect offers over 80 % protection.

A weak health system with many inadequacies (such as lack of equipment, drugs and other commodities, and a shortage of human resources) poses serious risks. While the DOTS expansion initiative, which commenced in 2002, has had a remarkable impact on TB case detection, provision of DOTS-plus to contain drug-resistant TB has been lagging behind. Surveillance and care for drug-resistant TB should be expedited. The need to urgently implement agreed upon interventions is crucial. These interventions include establishing and operating National and Zonal TB Reference Laboratories in the six health zones. Each should have the capacity to do cultures and drug susceptibility testing with both automated (BACTEC/MGIT) and nonautomated systems (LJ medium). They should be networked and provide oversight to state TB programs. Additionally, human resource workers should be trained to run the program at the tertiary level and to cascade it down to lower levels of TB services.

To facilitate achievement of MDG TB control targets, substantial improvement is necessary at all three tiers of government. This is especially required in the areas of funding, optimizing resource utilization, coordination, quality of services, and health sector reforms. Participation can be improved by promoting the community components of healthcare interventions like DOTS, Community TB Care, HIV/AIDS (community ART/home-based care), and Rollback Malaria. These health concerns have to be pursued along with improving literacy levels and poverty alleviation.

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Part II

Chapter 7
Diagnosis of Tuberculosis: Current Pipeline, Unmet Needs, and New Developments

Claudia M. Denkinger and Madhukar Pai

The diagnosis of tuberculosis (TB) is essential for the adequate treatment of an individual patient infected with TB and the control of TB at a population level. Countries with the highest TB prevalence throughout the world primarily rely on passive case-finding. The first step to the diagnosis of TB therefore requires the patient to present with signs and symptoms of TB, typically 2 weeks of cough and fever. There is often a delay in this first step. This is most commonly due to the patient's lack of knowledge about the disease and its presentation, stigma associated with TB or related diseases (i.e., human immunodeficiency virus (HIV)), trials of alternative treatments (i.e., traditional healers), and limited access to healthcare services (Finnie et al. 2011; Sreeramareddy et al. 2014). Further delay in the diagnosis may be caused by the healthcare provider not suspecting TB, particularly if the presentation is atypical (Finnie et al. 2011; Meintjes et al. 2008; Maciel et al. 2010). If TB is suspected in a patient, the next barrier to diagnosis consists of a lack of appropriate tools to establish the diagnosis accurately and in a timely manner, particularly in resource-poor settings where TB is most rampant.

This chapter describes the currently available tests for diagnosis of both latent and active TB as well as new developments in diagnostic tests that hold promise. Significant advancements have been made in the field of TB diagnostics; there are now more diagnostic tests on the market and endorsed by the World Health

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Organization (WHO) than ever before (Table 7.1) and backed by evidence from more than 50 systematic reviews (available at www.tbevidence.org). Despite that, there are still gaps in the pipeline, particularly in respect to a point-of-care test that could be used in resource-poor settings (Fig. 7.1) (WHO 2012; Cobelens et al. 2012).

7.1 Diagnosis of Latent TB

About one-third of the world's population is infected with TB. Only a small percentage (5–10 %) of the infected individuals will develop disease, most commonly within the first 2 years after infection (Hill et al. 2008; Lienhardt et al. 2010). The tuberculin skin test (TST) was developed by von Pirquet at the turn of the century (von Pirquet 1907) and has been used for the diagnosis of latent TB infection (LTBI) ever since. In 2005, the interferon-γ release assays (IGRAs) were added to the diagnostic armamentarium for LTBI. The TST and IGRA both evaluate the presence of mycobacteria-specific T cell responses to recent or remote sensitization. Therefore neither of the two tests can distinguish between individuals with LTBI, active TB, or even past TB.

For the TST a purified protein derivative (precipitate of filtrates from sterilized, concentrated mycobacterial cultures) is injected intradermally and a delayed type hypersensitivity reaction to the precipitate in the form of local skin induration is measured. The IGRAs detect the release of interferon-γ from T cells following stimulation by antigens of the region of difference 1 (ESAT-6, CFP-10, and TB7.7). These antigens are more specific for the *Mycobacterium tuberculosis* (MTB) complex as they are not shared with the Bacille Calmette–Guérin (BCG) vaccine strains or most other nontuberculous mycobacteria (NTM) (e.g., *Mycobacterium avium*) (Andersen et al. 2000). IGRAs therefore are useful for the evaluation of LTBI in BCG-vaccinated individuals, particularly if BCG vaccination has been administered after infancy or multiple doses of BCG vaccine have been given.

The QuantiFERON-TB© Gold In-Tube (QFT-GIT, Cellestis Limited, Australia) uses an enzyme-linked immunosorbent assay (ELISA), and the TB-SPOT.TB© assay (Oxford Immunotec, UK) employs an enzyme-linked immunosorbent spot technique (ELISPOT) to detect the interferon-γ. Aside from the increased specificity, IGRAs have several additional advantages over a TST: (1) IGRAs require only one visit; (2) boosting effect is eliminated by ex-vivo testing; (3) interpretation is objective and results can be available within 24–48 h. However, more recent data highlight issues with reproducibility which limits the use of IGRAs especially for repeat testing (Pai et al. 2014; Dorman et al. 2014). The TST, in contrast, is the simpler test (that requires no laboratory infrastructure) and is used more easily in remote settings and is less expensive. A comparison between the two tests is summarized in Table 7.2.

A World Atlas of BCG Policies and Practices (www.bcgatlas.org) reviews variations of BCG use in different countries and can help clinicians to determine the patients in whom IGRA testing may be valuable in addition to or in replacement of the TST (Zwerling et al. 2011). A web-based algorithm also has been developed to aid in the interpretation of TST and IGRAs (http://www.tstin3d.com).

Table 7.1 Recent WHO policies and statements on TB diagnostics

Year policy made	Purpose of testing	Diagnostic test or approach	WHO recommendations
2007	Case detection and DST	Liquid Media for Culture and DST	WHO recommends, as a stepwise approach
			• The use of liquid medium for culture and DST in middle- and low-income countries
			• The rapid species identification to address the needs for culture and DST
			Taking into consideration that liquid systems will be implemented in a phased manner, integrated into a country-specific comprehensive plan for laboratory capacity strengthening
2007	Case detection	Definition of a New Sputum Smear-Positive TB Case	The revised definition of a new sputum smear-positive pulmonary TB case is based on the presence of at least one AFB+ in at least one sputum sample in countries with a well-functioning EQA system
2007	Case detection	Reduction of Number of Smears for the Diagnosis of Pulmonary TB	WHO recommends the number of specimens to be examined for screening of TB cases can be reduced from three to two in places where a well-functioning EQA system exists, the workload is very high, and human resources are limited
2008	DST	Molecular Line Probe Assays for Rapid Screening of Patients at Risk of MDR-TB	The use of line probe assays is recommended by WHO, with the following guiding principles
			• Adoption of line probe assays for rapid detection of MDR-TB should be decided by Ministries of Health within the context of country plans for appropriate management of MDR-TB patients, including the development of country-specific screening algorithms and timely access to quality-assured second-line anti-TB drugs
			• Line probe assay performance characteristics have been adequately validated in direct testing of sputum smear-positive specimens and on isolates of *Mycobacterium tuberculosis* (MTB) complex grown from smear-negative and smear-positive specimens. Direct use of line probe assays on smear-negative clinical specimens is not recommended
			• The use of commercial line probe assays, rather than in-house assays, is recommended to ensure reliability and reproducibility of results, as in-house assays have not been adequately validated or used outside limited research settings
			• Adoption of line probe assays does not eliminate the need for conventional culture and DST capability; culture remains necessary for definitive diagnosis of TB in smear-negative patients, while conventional DST is required to diagnose XDR-TB
			• As current line probe assays only detect resistance to rifampin and/or isoniazid, countries with documented or suspected cases of XDR-TB should establish or expand conventional culture and DST capacity for quality-assured susceptibility testing of second-line drugs, based on current WHO policy guidance
2009	Case detection	LED-based microscopy	WHO recommends:
			• Conventional fluorescence microscopy should be replaced by LED microscopy in all settings. LED microscopy should be phased in as an alternative for conventional ZN microscopy in both high- and low-volume laboratories
			• The switch to LED microscopy should be carried out through a carefully phased implementation plan, using LED technologies that meet WHO specifications

(continued)

Table 7.1 (continued)

Year policy made	Purpose of testing	Diagnostic test or approach	WHO recommendations
2009	DST	Noncommercial culture and DST methods	WHO recommends that selected noncommercial culture and DST methods be used as *an interim solution* in resource-constrained settings, in reference laboratories or those with sufficient culture capacity, while capacity for genotypic and/or automated liquid culture and DST are being developed. With due consideration of the above issues, WHO endorses the selective use of one or more of the following noncommercial culture and DST methods
			• Microscopically observed drug susceptibility (MODS) for rapid screening of patients suspected of having MDR-TB, under clearly defined programmatic and operation conditions, and once speciation concerns have been adequately addressed without compromising biosafety
			• The nitrate reductase assay (NRA) for screening of patients suspected of having MDR-TB, under clearly defined programmatic and operation conditions, and acknowledging that time to detection of MDR in indirect application would not be faster (but less expensive) than conventional DST methods using commercial liquid culture or line probe assays
			• Colorimetric redox indicator (CRI) methods as indirect tests on MTB isolates from patients suspected of having MDR-TB, under clearly defined programmatic and operation conditions and acknowledging that time to detection of MDR would not be faster (but less expensive) than conventional DST methods using commercial liquid culture or line probe assays
2011	Case detection and DST	Xpert MTB/RIF	WHO recommends two indications for the Xpert MTB/RIF
			• Xpert MTB/RIF should be used *as the initial diagnostic test* in individuals suspected of MDR-TB or HIV-associated TB (strong recommendation)
			• Xpert MTB/RIF may be used as a follow-on test to microscopy in settings where MDR and/or HIV is of lesser concern, especially in smear-negative specimens (conditional recommendation, recognizing major resource implications)
			Xpert MTB/RIF is suitable for use at district and subdistrict level. However, Xpert MTB/RIF technology does not eliminate the need for conventional microscopy culture and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampin
			In addition, it is recommended that in settings or patient groups where rifampin resistance is rare, Xpert MTB/RIF results indicating rifampin resistance should be confirmed by conventional DST or line probe assays
			In addition, several operational conditions need to be met for successful implementation of Xpert MTB/RIF: stable electrical supply, a maximum ambient operating temperature of 30 °C for the GeneXpert device, security against theft, dedicated trained personnel, adequate storage space, annual calibration of the instrument by a commercial supplier, and biosafety precautions similar to those for direct sputum microscopy should all be in place
2011	Case detection	Same-day diagnosis of TB by microscopy	Same-day diagnosis refers to consecutive sputum specimens from the same patient being examined—and results provided to health facilities—on the same day. WHO recommends that implementation of a "same-day diagnosis" ("front-loaded microscopy") strategy be preceded by a detailed situation assessment of the programmatic, logistic, and operational implications at country level and supported by a carefully phased implementation plan

2011	Case detection	Commercial serological (antibody) detection tests	Commercial serological tests provide inconsistent and imprecise findings resulting in highly variable values for sensitivity and specificity. There is no evidence that existing commercial serological assays improve patient-important outcomes, and high proportions of false-positive and false-negative results adversely impact patient safety. Overall data quality was graded as very low and it is strongly recommended that these tests not be used for the diagnosis of pulmonary and extrapulmonary TB
2011	Latent TB	IGRAs	Active TB: IGRAs (and the TST) should not be used in low- and middle-income countries for the diagnosis of pulmonary or extrapulmonary TB, nor for the diagnostic workup of adults (including HIV-positive individuals) suspected of active TB in these settings (strong recommendation)
			IGRAs should not replace the TST in low- and middle-income countries for the diagnosis of latent TB infection in children, nor for the diagnostic workup of children (irrespective of HIV status) suspected of active TB in these settings (strong recommendation)
			IGRAs should not replace the TST in low- and middle-income countries for the diagnosis of latent TB infection in individuals living with HIV infection, in screening of latent TB infection in adult and pediatric contacts, outbreak investigations or in healthcare worker screening programs.
			Neither IGRAs nor the TST should be used in low- and middle-income countries for the identification of individuals at risk of developing active TB (strong recommendation)
2013	Case detection and DST	Xpert MTB/RIF	Updated recommendations
			• Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults and children presumed to have TB (conditional recommendation acknowledging resource implications, high-quality evidence)
			• Xpert MTB/RIF should be used rather than conventional microscopy, culture, and DST as the initial diagnostic test in adults and children presumed to have MDR-TB or HIV-associated TB (strong recommendation, high-quality evidence)
			• Xpert MTB/RIF may be used as a follow-on test to microscopy in adults presumed to have TB but not at risk of MDR-TB or HIV-associated TB, especially in further testing of smear-negative specimens (conditional recommendation acknowledging resource implications, high-quality evidence)
			• Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from patients presumed to have TB meningitis (strong recommendation given the urgency of rapid diagnosis, very low quality of evidence)
			• Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from patients presumed to have extrapulmonary TB (conditional recommendation, very low quality of evidence)

Source: Pai et al. (2010) [modified and reproduced with permission] *AFB* acid fast bacilli, *DST* drug susceptibility testing, *EQA* external quality assurance, *HIV* human immunodeficiency virus, *IGRA* Interferon-gamma release assay, *LED* light-emitting diode, *MDR-TB* multidrug-resistant tuberculosis, *TB* tuberculosis, *TST* tuberculin skin test, *WHO* World Health Organization, *XDR-TB* extensively drug-resistant TB, *ZN* Ziehl–Neelsen

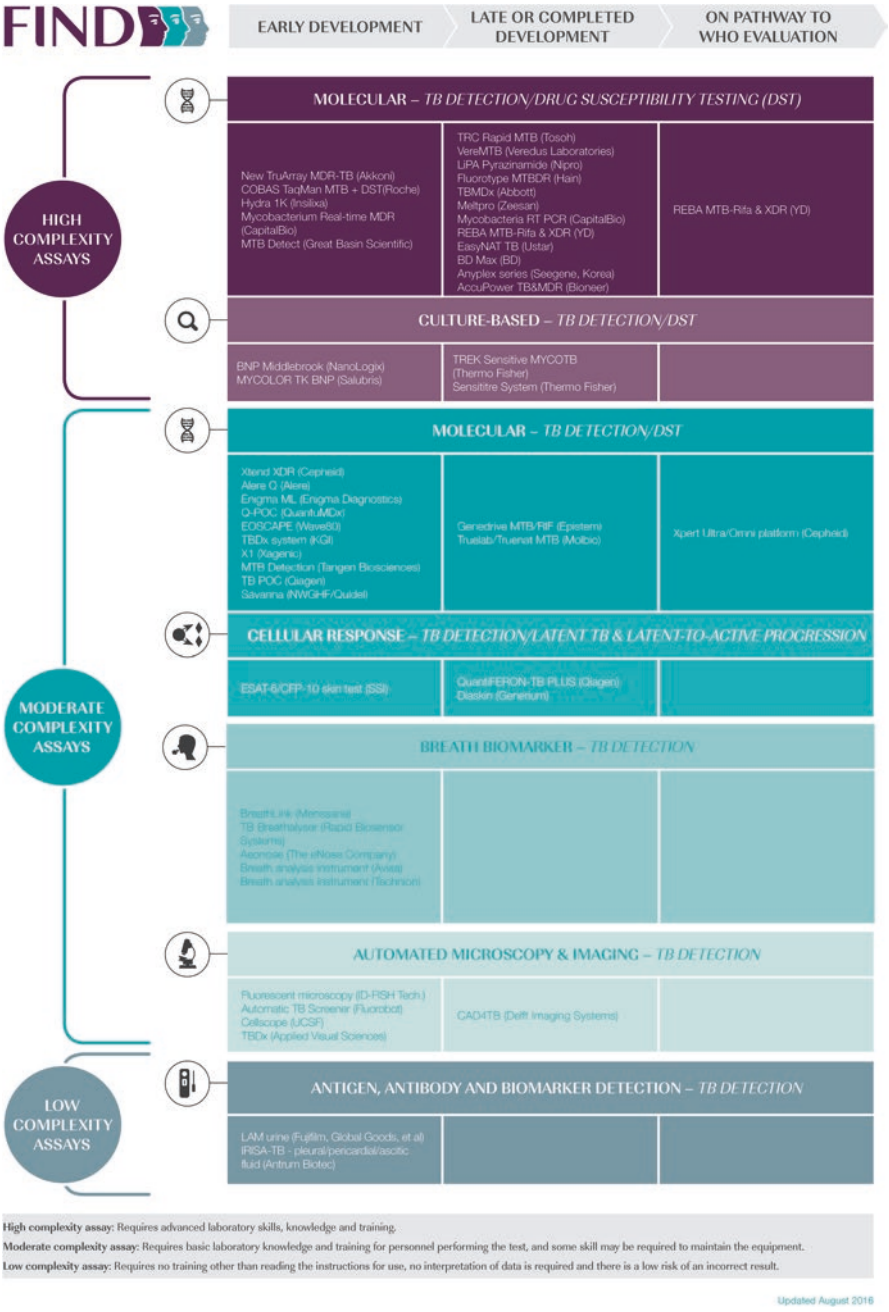

Fig. 7.1 TB diagnostics pipeline (2016). Source: WHO report 2012 (WHO 2012). This image is reproduced with the permission of FIND, Geneva.

Table 7.2 Comparison of TST and IGRA

	TST	IGRA
+	• Simple, low-tech test	• IGRA requires only one visit
	• Can be done by trained HCW in remote locations	• Boosting effect eliminated by ex-vivo testing
	• Effect of BCG on TST results is minimal if vaccination is given at birth and not repeated	• IGRA interpretation is objective
	• Longitudinal studies have demonstrated its predictive value	• IGRA results can be available within 24–48 h
		• No cross-reactivity with BCG and less with NTM
–	• TST may give false-negative reactions due to infections, live virus vaccines, and other factors	• IGRA requires a blood draw (problem in young children)
	• TST may give false-positive results because of BCG and NTM	• Require lab capacity to perform test
	• Requires an intradermal injection	• Risk of exposure to blood-borne pathogens
	• Can rarely cause adverse reactions (acute reactions, skin blistering, and ulceration)	• Interpretation of serial IGRA is complicated by frequent conversions and reversions, and lack of consensus on optimum thresholds for conversions and reversions
	• TST interpretation is subjective	
	• TST requires 48–72 h for a valid result	

Source: Pinto et al. (2011) [modified and reproduced with permission] *BCG* Bacille Calmette-Guérin vaccine, *HCW* health care workers, *IGRA* Interferon-gamma release assay, *NTM* Nontuberculous mycobacteria, *TST* tuberculin skin test

IGRAs are utilized increasingly particularly in low-incidence countries in addition to the TST upfront, particularly in immunocompromised patients with high risk for progression to active TB (to increase sensitivity of LTBI detection) or in a two-step approach primarily in BCG-vaccinated individuals (to increase specificity) (Denkinger et al. 2011; Cattamanchi et al. 2011a; Smith et al. 2011). In some countries, IGRAs have replaced the TST or are used as an equivalent alternative (Denkinger et al. 2011) (Table 7.3).

However, both the TST and the IGRAs have limited ability to predict the individuals who are going to progress to active TB and therefore would benefit most from preventative isoniazid therapy (Rangaka et al. 2012). Recent longitudinal studies show that a large fraction of those positive with TST or IGRAs do not progress to active disease. Therefore, new biomarkers are needed to predict these patients more accurately (Cobelens et al. 2012; Wallis et al. 2010).

7.2 Diagnosis of Active TB

7.2.1 Pulmonary TB

Pulmonary TB is the most common presentation of TB disease. Established diagnostic methods are outlined in Table 7.4.

Table 7.3 Overview of recommendations found in guidelines and position papers

Overview of common recommendations for particular indications	Guideline or position statement[a]
Active TB in adults	
For the use of IGRAs but only as an adjunct (some guidelines specify the use only when other diagnostic tests have been unrevealing)	ECDC, USA (CDC), UK, France, Australia, Japan, Netherlands, Norway, Bulgaria, Portugal, Denmark, Austria
Active TB in children	
For the use of IGRAs but only as an adjunct (some guidelines specify the use only when other diagnostic tests have been unrevealing)	ECDC, Canada, USA (CDC and AAP), UK, Switzerland, Australia, Saudi Arabia, Netherlands, Norway, Bulgaria, Portugal, Croatia, Denmark, Austria
Contact investigation in adults	
TST followed by IGRA if TST positive (either IGRA only in BCG-vaccinated persons or independent of BCG vaccine)	Canada (low-risk contacts), Germany, Italy, Switzerland, Spain, Saudi Arabia, Netherlands, Norway, Bulgaria, Portugal, Ireland, ECDC (low-incidence countries), and UK
TST alone	WHO, Brazil, ECDC (high-incidence countries)
Contact investigation in children	
TST followed by IGRA if TST positive (some specify TST alone in children 0–4 years old or dependent on BCG vaccination status)	Canada (low-risk contacts), Japan, Ireland, USA (AAP), Germany, Italy, Spain, Saudi Arabia, Netherlands, Bulgaria, and for children >5 years of age only in Portugal and UK (<5, TST and if negative IGRA)
TST alone	WHO, ECDC, France, Brazil, Switzerland
LTBI screening for HIV-infected patients	
Both TST and IGRA	ECDC, Portugal, Croatia, Slovakia, Netherlands, USA (if either initial test negative), South Korea, UK
IGRA alone	Switzerland, Bulgaria, France, UK (if CD4 200–500)
TST alone	WHO, Brazil
LTBI screening in persons starting on TNFα-inhibitors	
Both TST and IGRA	ECDC, UK (alternatively IGRA alone), USA (if either initial test negative), Portugal, Croatia, Czech Republic, Slovakia, Netherlands, South Korea, Ireland (TST preferred)

Source: Denkinger et al. (2011) [modified and reproduced with permission]
AAP American Academy of Pediatrics, *BCG* Bacille Calmette-Guérin, *CDC* US Centers for Disease Control and Prevention, *ECDC* European Centre for Disease Prevention and Control, *HIV* human immunodeficiency virus, *IGRA* Interferon-gamma release assay, *TST* tuberculin skin test, *WHO* World Health Organization

[a] Some countries/organizations are listed more than once because their recommendations vary across risk groups

Table 7.4 Established diagnostic methods for pulmonary TB

Technique	Resource need	Time	Sensitivity[a]	Comment
Radiography	Low	<2 h	85–95 %	Sensitivity limited especially in HIV-coinfected individuals; specificity limited
Sputum-microscopy	Low	<2 h	60–70 %	Can be further enhanced with pretreatment (i.e., bleach, centrifugation)
Sputum-fluorescence microscopy	High	<2 h	70–80 %	Can be modified with LED and applied in resource-poor settings; good for high-volume throughput
Sputum-culture	Low	Weeks	80–100 %	Gold standard; decreased incubation time with liquid media or thin-layer agar
Sputum-NAA tests	High	Hours to days	50–70 % in smear-negative, 100 % in smear-positive	Sensitivity lower than culture but improved compared to microscopy for recent developments (i.e., Xpert MTB/RIF); automated systems also increase applicability in moderate- to low-resource settings

HIV human immunodeficiency virus, *NAA* nucleic acid amplification, *LED* light-emitting diode
[a]On average; in individuals without HIV

7.2.1.1 Radiography

The initial step in the diagnosis of pulmonary TB is often a chest X-ray (CXR). While CXR is reasonably sensitive, it lacks specificity and thus overreliance on chest radiography can result in overtreatment (Rabinovitch and Pai 2013). Thus, all patients with CXR abnormalities must undergo microbiological investigations to confirm TB disease. Advanced HIV can alter the presentation of TB on CXR. Classical signs are often not present and even a completely normal CXR has been reported in up to 20 % of patients (Geng et al. 2005). The radiographic features of TB on chest imaging are classically divided into those of primary TB, reactivation TB, miliary TB, and tracheobronchial TB (Jeong and Lee 2008).

Primary TB is most frequently seen in children. The common abnormality on CXR is lymphadenopathy which is usually unilateral in the hilar or the paratracheal region (Leung et al. 1992). The often nodular abnormality in the lung parenchyma, called the Ghon's complex, and a unilateral pleural effusion are less frequent (Woodring et al. 1986). Miliary TB occurs more frequently in children in the context of primary infection and in adults in the context of reactivation of infection. It is caused by a hematogenous spread of MTB and on CXR is characterized by a large number of 1–3 mm small nodules (similar to millet seeds thus the term "miliary") are seen (Fig. 7.2a) (Jeong and Lee 2008).

The radiographic characteristic of reactivation pulmonary TB is a focal consolidation most commonly involving the apical and posterior segments of the upper

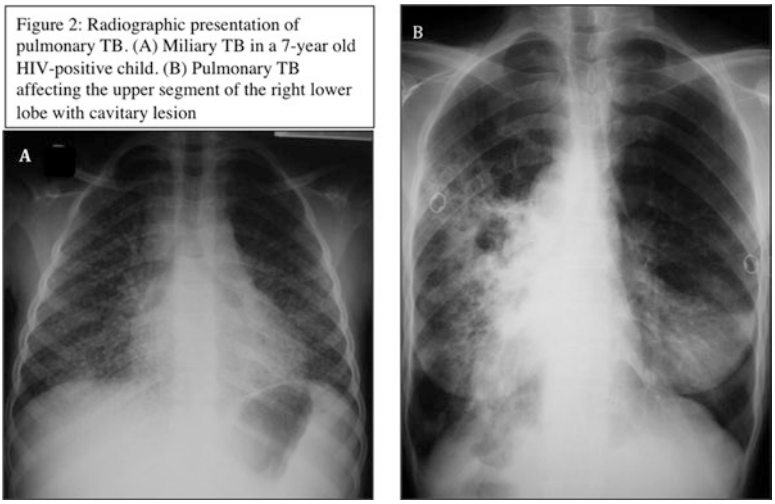

Fig. 7.2 Radiographic manifestations of pulmonary TB. (**a**) Miliary TB in a 7-year-old HIV-positive child. (**b**) Pulmonary TB affecting the upper segment of the right lower lobe with cavitary lesion

lobes and/or the superior segments of the lower lobes (Fig. 7.2b). Cavities can be present in 20–45 % of cases. A tuberculoma, which is characterized as a well-defined round lesion, is less frequently seen (about 5 %) (Krysl et al. 1994). Tracheobronchial disease often presents with thickening and luminal narrowing of the major airways (Moon et al. 1997).

7.2.1.2 Smear Microscopy

Microscopic visualization of the mycobacteria with Ziehl–Neelsen or Kinyoun stain is taking advantage of the bacteria's ability to retain certain dyes in the presence of acid (Ehrlich 1882). This remains the most frequently used, inexpensive, and rapid diagnostic method with low technical requirements. The sensitivity of a sputum smear ranges between 50 and 70 % and can be further enhanced by simple physical or chemical sputum processing with centrifugation, sedimentation, and bleaching (Steingart et al. 2006a; Cattamanchi et al. 2010). Specificity of smear microscopy is very high in high TB prevalence environments and false positives are uncommon.

For many years three sputum specimens on separate days were recommended for the diagnosis of TB. However, these strategies have been hampered by large numbers of patients not returning for follow-up. The yield of the third sputum specimen, however, has been estimated to be only 2–5 % on average (Mase et al. 2007; Bonnet et al. 2007), which led the WHO to endorse a policy reducing the minimum number of sputum specimens examined per patient from three to two

(WHO 2010a) (Table 7.1). More efforts are under way to optimize front-loaded (also called same-day) smear microscopy with two specimens examined 2 h apart (Ramsay et al. 2009; Cuevas et al. 2011) or one specimen examined twice (Cattamanchi et al. 2011b). All of these strategies are expected to increase the case-finding, as the number of patients lost to follow-up is estimated to be smaller than the number of patients not detected to have TB due to slightly decreased sensitivity. In children it is often difficult to obtain a sputum sample and a gastric aspirate or induced sputum specimen can be examined instead with the same staining methods (Zar et al. 2005).

Fluorescence microscopes (FM), now widely used in resource-rich countries, have further increased the sensitivity of smear microscopy by 10 % on average and also decreased the time needed to examine one smear. The latter is especially important when a high volume of smears is assessed on a daily basis (Steingart et al. 2006b). However, FM comes at an increased cost. Light-emitting diodes (LED) represent a more suitable alternative for resource-poor settings as they require less power, are less costly, do not require a dark room, and have a longer life span than FM. A number of studies suggest that sensitivity for LED microscopes is slightly increased or at least comparable to light microscopy and operator time is less (Albert et al. 2010; Shenai et al. 2011; Bonnet et al. 2011) which resulted in the WHO endorsement of this technique (WHO 2010b) (Table 7.1).

7.2.1.3 Culture-Based Methods

Identifying MTB on culture remains the gold standard for diagnosis of active TB. Classically the egg-based Löwenstein–Jensen medium has been used for culture of MTB; however, the time to growth on average is 4 weeks. Newer solid media culture methods include the thin-layer agar technique that uses 7H10/7H11 agar plates inoculated with sputum specimens that are examined for microcolonies under a microscope (Mejia et al. 1999). This technique provides results faster (on average 2 weeks but longer in smear-negative samples) than traditional Löwenstein–Jensen culture. Both culture media allow for simultaneous phenotypic resistance testing with high sensitivity and specificity through direct inoculation of antibiotic-containing media using the proportion method (Tables 7.4 and 7.5).

Liquid cultures, developed over the last two decades, take on average about 2 weeks and appear to be about 10 % more sensitive than solid media cultures (Cruciani et al. 2004), which led the WHO to endorse these techniques in 2009 (WHO 2009) (Table 7.1). Automated liquid cultures detect changes in oxygen, CO_2, or radioactivity due to growth of mycobacteria (e.g., BACTEC™). The ability of mycobacteria to metabolize nitrate (i.e., nitrate reductase assay) or to produce a color change with certain growth indicators (e.g., alamar blue) is being investigated for use in low-resource settings as well (Angeby et al. 2002; Martin et al. 2007). Once growth of mycobacteria is detected, further identification and testing is pursued with molecular methods.

Table 7.5 Diagnostics for drug-resistance testing

Technique	Time	Resistance detection	Comment
Culture-based tests	Weeks	First- and second-line drugs	Commercialized; most culture techniques (including solid and liquid media based tests) have been successfully adapted for resistance testing most commonly using the proportion technique; faster when performed directly from smear-positive specimens
Colorimetric and nitrate reductase assays	Weeks	Rifampin and isoniazid	Non-commercialized; culture based; highly sensitive and specific for resistance testing in culture isolates
Microscopic observation drug susceptibility (MODS)	Weeks	Rifampin and isoniazid	Commercialized; culture based; highly sensitive and specific detection of rifampin resistance and slightly less for isoniazid
Line probe assays	Hours	Rifampin and isoniazid	Commercialized; PCR based; highly sensitive and specific for rifampin resistance, slightly less sensitive for isoniazid and variable sensitivity for second-line drugs; can be done on cultures or directly on sputum samples
GeneXpert	Hours	Rifampin	Commercialized; PCR-based with molecular beacons; highly sensitive and specific directly on sputum samples

Automated liquid culture systems (e.g., MGIT 960, BD, Sparks, USA) followed by molecular identification methods (i.e., with line probe assay or transcription-mediated amplification tests) are being employed across the developed world but are in their current form not practical in low-resource settings. Simple lateral flow tests for antigen detection of MTB-specific antigen MPB-64 would be an alternative for low-resource settings and have been applied to organisms isolated in solid or liquid culture with high accuracy (Abe et al. 1999; Hasegawa et al. 2002).

Microscopic observation drug susceptibility (MODS) testing represents an alternative to automated liquid cultures and takes advantage of the characteristic pattern of growth that MTB demonstrates in liquid culture (i.e., cording) (Caviedes et al. 2000). MODS testing is a manual liquid culture technique that only requires basic laboratory equipment and has been validated in different countries under low-resource conditions (Minion et al. 2010). However, MODS requires substantial training and standardization which makes it difficult to scale-up across countries.

Liquid culture techniques also allow for simultaneous testing of drug susceptibility through direct inoculation of the specimen in media with antibiotics. The performance characteristics of the liquid culture-based drug susceptibility testing are excellent for rifampin and very good for isoniazid; however, they are variable for second-line drugs (Table 7.5) (Bwanga et al. 2009; Horne et al. 2013).

The thin-layer agar, nitrate reductase assay and MODS are certainly promising steps towards more rapid, simplified, and sensitive testing in low-resource settings with high rates of drug-resistant TB. Unfortunately, scale-up of these methods has

been poor as requirements for laboratory capacity, training, standardization, and quality assurance remain substantial.

7.2.1.4 Nucleic Acid Amplification Tests

Nucleic acid amplification (NAA) tests detect MTB through amplification of specific nucleic acid regions and can be used on sputum directly. The NAA tests are highly sensitive (about 100 %) in smear-positive pulmonary TB and also highly specific which allows the clinician to differentiate between MTB and NTM (Flores et al. 2005). The sensitivity is lower in smear-negative patients (50–80 %) (Flores et al. 2005; Guerra et al. 2007; Dinnes et al. 2007), low in extrapulmonary specimens, and even lower (39 %) in high HIV prevalence settings (Davis et al. 2011). The test therefore does have additional value for the diagnosis of pulmonary TB in high-burden settings; however, it cannot function as a rule out test.

Line probe assays (LPAs) are strip tests using polymerase-chain-reaction (PCR) and reverse hybridization methods for the rapid differentiation of mycobacteria and the detection of drug-resistance mutations at the same time from culture. The most frequently used test is the GenoType MTBDR assay (Hain Lifescience, Germany). LPAs have excellent sensitivity and specificity for rifampin resistance; however, results for isoniazid resistance have been variable (Table 7.5) (Bwanga et al. 2009; Ling et al. 2008). The GenoType MTBDR assay is WHO-endorsed, and is currently being scaled-up in many high-burden countries through the EXPAND-TB project. Newer versions of the GenoType MTBDR test are also undergoing evaluation for the diagnosis of XDR-TB and might hold promise (Barnard et al. 2012; Feng et al. 2013). A disadvantage of these tests is that they require skilled laboratory personnel as well as adequate quality control. They also do not eliminate the need for culture methods given the limited sensitivity for the diagnosis of TB in smear-negative patients. The role of these tests in resource-poor settings therefore is limited.

An exciting newer development is the Xpert MTB/RIF assay, an automated test for the diagnosis of MTB and resistance to rifampin on sputum specimens using real-time PCR in combination with molecular beacons (Boehme et al. 2010) via the GeneXpert platform (Cepheid, Sunnyvale, CA, USA). The Xpert MTB/RIF test has excellent sensitivity for detecting MTB on smear-positive TB (98 %), moderate sensitivity for smear-negative sputum specimens (67 %), and high specificity (99 %). Detection of resistance to rifampin also is highly accurate (95 % sensitivity, 98 % specificity; Table 7.5) (Steingart et al. 2014). The advantage of the Xpert MTB/RIF, in contrast to conventional NAA tests, that it requires minimal training as it is largely automated, has good biosafety characteristics, and gives results in less than 2 h. The WHO endorsed the Xpert MTB/RIF initially in 2011 and recently updated its guidelines to suggest Xpert as an initial diagnostic test in all individuals suspected of having TB if financial considerations allow and strongly recommends its use as a primary test in settings where MDR-TB or HIV is prevalent (WHO 2011a, 2013a) (Table 7.1). Scale-up of the Xpert MTB/RIF in high-burden settings is currently under way in over 90 countries worldwide (WHO 2013b). However, the

limitation of Xpert is its applicability only at the district level and above; a smear-replacement test at the level of the microscopy center or below remains a focus of research (Denkinger et al. 2013).

7.2.2 Extrapulmonary TB

Extrapulmonary TB (EPTB) is difficult to diagnose and requires high clinical suspicion. Histopathology assessing for caseating granulomas as well as staining for MTB and culture remains the gold standard of diagnosis. NAA tests on diagnostic samples other than the sputum have variable and on average lower sensitivity than in sputum samples but good specificity across studies for TB pleuritis and meningitis (Pai et al. 2003, 2004). Xpert, however, appears to hold promise for the diagnosis of EPTB from lymph node samples, gastric fluid, and tissue, with sensitivities in the range of 80 % as well as of TB meningitis from cerebrospinal fluid with sensitivities on average of 55 %. These findings, plus the advantage of rapid results, led the WHO to recently endorse the test for these indications (WHO 2013a).

Adenosine deaminase (ADA) testing is available on pleural, peritoneal, and cerebrospinal fluid. Its sensitivity for the diagnosis of TB on pleural fluid was found to be high (88–100 %) with moderate specificity (83–97 %) (Dinnes et al. 2007; Greco et al. 2003; Goto et al. 2003). The sensitivity can be further increased when the test is combined with other nonspecific markers of inflammation such as interferon-γ, C-reactive protein (CRP), or lysozyme (Dinnes et al. 2007; Greco et al. 2003; Valdes et al. 1993; Garcia-Pachon et al. 2005). ADA testing for the diagnosis of TB meningitis is hampered by the lack of specificity, as elevations in the enzyme are observed in bacterial meningitis as well; however, the levels detected in TB meningitis are typically higher. The sensitivity and specificity therefore are highly dependent on what cutoff is chosen (Xu et al. 2010; Tuon et al. 2010). For peritoneal TB, sensitivities and specificities of ADA appear to be high (100 % and 97 %) in a meta-analysis of 12 prospective studies, suggesting that it is a useful marker on peritoneal fluid (Riquelme et al. 2006). CRP has also been examined in whole blood in patients with smear-negative pulmonary TB and might be helpful as an adjunct test (Wilson et al. 2011).

There are limited data to support the use of IGRAs in the diagnosis of active TB and some guidelines clearly discourage use of IGRAs for active TB diagnosis in adults (Metcalfe et al. 2011; Sester et al. 2011). If used at all, IGRAs are generally considered as an adjunct test in addition but not replacing the standard microbiological and radiographic tests (Denkinger et al. 2011).

ELISPOT testing for ESAT-6 and CFP-10 can also be considered on samples other than blood (e.g., cerebrospinal, pericardial, peritoneal, or pleural fluid). In one study the overall sensitivity and specificity were 79.8 % and 81.6 %, respectively (Liao et al. 2009). On samples from a bronchoalveolar lavage (BAL) studies have shown a sensitivity of 91 % and specificity of 80 % in smear-negative cases, respectively (Jafari et al. 2009).

7.2.3 *Other Developments and Prospects for a Point-of-Care Test*

Lack of an accurate point-of-care (POC) test for active TB remains a big gap in the existing diagnostics pipeline, although much work is being done to develop simple tests based on antigen or antibody detection and other biomarkers (Dheda et al. 2013; Pai et al. 2012). Several NAA technologies are being developed for rapid POC TB diagnosis. Loop-mediated isothermal amplification (LAMP) is a simple method for DNA amplification that does not require a thermocycler or detection system and holds promise for resource-poor settings; however, the sensitivity of early generation tests on smear-negative samples was limited (Boehme et al. 2007). Other fast-followers to Xpert, such as the TrueNAT (Molbio Diagnostics Private Ltd., India) and Gendrive (Epistem, UK) or EasyNAT TB (Ustar Biotechnologies, China) just to mention few, are aiming to target the market at the microscopy center level, but so far all of the fast-follower technologies are lacking a fully integrated system.

Antigen-based diagnosis certainly has the potential for implementation at the POC. Lipoarabinomannan (LAM) is a cell wall-associated glycolipid of MTB. Its detection in urine, with an ELISA-based method initially and now with a lateral flow device, has shown promising results in HIV-positive patients with low CD4 counts (sensitivity exceeds 60 % in HIV-positive patients with CD4 counts <50 cells/mm^3) (Minion et al. 2011). Serological tests certainly have great potential for POC testing if biomarkers are identified that can be targeted; however, existing commercial tests are of little clinical value because of poor sensitivity and specificity. This lead to the WHO issuing a recommendation against the use of these tests (Dowdy et al. 2011; Steingart et al. 2011; WHO 2011b) (Table 7.1).

Detection of volatile organic compounds in the breath might also be a possible option for the diagnosis of pulmonary TB at the POC; however, studies have shown only moderate sensitivity and limited specificity (Phillips et al. 2010). A new approach to the diagnosis of TB is the detection of cell-free fragments of mycobacterial DNA in the urine (Green et al. 2009). The detection of the transrenal DNA showed limited and highly variable sensitivity in early studies (14–57 %) (Torrea et al. 2005; Rebollo et al. 2006). However, with newer generations of NAA testing and optimization of collection, extraction, and storage methods, the sensitivity might substantially improve (Green et al. 2009).

Other new technologies could enhance the diagnosis of TB if the appropriate biomarkers are targeted and the technologies are adapted for use at lower levels of the healthcare system but thus far these technologies are only available in reference laboratories. Examples of such technologies are (1) nanoparticle-based magnetic resonance detection (Lee et al. 2009); (2) mass spectrometry (Agranoff et al. 2006); or (3) high performance liquid chromatography (HPLA) (Glickman et al. 1994). Improvements in sequencing technologies furthermore may facilitate the detection of drug resistance in the years to come.

7.3 Need for New Tools

Although considerable advance has been made in the diagnosis of active and latent TB and more tests are now on the market or in development than ever before, there are still significant gaps in the diagnostic pipeline (Fig. 7.1). Most notable is the lack of a simple, rapid, and inexpensive POC test that can be used in resource-poor settings. Ideally the test would be able to diagnose both pulmonary and extrapulmonary TB in adults and children. However, a POC test for pulmonary TB alone in adults would address the majority of infections and also limit the greatest source of further transmission. In addition, a reliable, fast, and simple test for first- and second-line drug resistance is urgently needed to ensure appropriate treatment of MDR- or XDR-TB and prevent further spread of this difficult to treat disease.

The identification of new biomarkers for different stages of infection and disease is necessary to allow clinicians to predict which patient will progress from one stage to the next and therefore would benefit the most from preventive treatment of LTBI (Wallis et al. 2010). Further developments in immunology, proteomics, and genomics are likely going to identify new biomarkers in the coming years (Barry et al. 2009; Fortune and Rubin 2010). Furthermore, the application of new technologies such as microfluidics and nanotechnology has potential to revolutionize POC diagnostics.

7.4 Conclusion

While the current diagnostic methods for TB are still limited, promising achievements have been made over the recent years and further developments are in sight. However, it is important to recognize that even new tools have limited impact unless the necessary evidence is collected and ultimately translated into practice to ensure the scale-up and appropriate use.

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Chapter 8
Current Options in Treatment and Issues in Tuberculosis Care in Low- and Middle-Income Countries

Anurag Bhargava and Dick Menzies

8.1 Introduction

We stand at a critical crossroads on the path of tuberculosis (TB) control. More than two decades ago, the World Health Organization (WHO) declared TB a global emergency. This declaration helped focus the attention of governments of high-incidence countries and the international health community on the problem of TB. In 1995, the WHO established a global strategy with targets of 70 % case detection and 85 % cure rates; this was expected to result in a 50 % reduction in TB incidence over 15 years (Kochi 1991). Although the 85 % target for cure rates has been achieved, the target for case detection rates has not, and global TB incidence has not declined as predicted (Obermeyer et al. 2008; Dowdy and Chaisson 2009). The current post-2015 WHO End TB Strategy has treatment-related goals which seem achievable in low-incidence countries but are ambitious for the high burden countries: 95 % reduction in deaths (compared to 2015) with 90 % reduction in incidence (below 10 cases per 100,000) by 2035 with an eventual elimination of TB (defined as less than 1 case per million population by 2050) (WHO 2013a). This goal is to be compared with current TB incidence in high burden countries like India and South Africa of 171 and 863 per 100,000 population, respectively (WHO 2014b).

In the absence of an effective vaccine to prevent infectious forms of TB in adults, the current global TB control strategy is based on case-finding and treatment.

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Table 8.1 Components of the DOTS strategy (WHO 1999)

• Government commitment to sustained TB control activities
• Case detection by sputum-smear microscopy for symptomatic patients self-reporting to health services
• Standardized treatment regimen of 6 to 8 months for at least all confirmed sputum-smear positive cases, with directly observed treatment (DOT) for at least the initial 2 months
• A regular, uninterrupted supply of all essential anti-TB drugs
• A standardized recording and reporting system that allows assessment of treatment results for each patient and of the TB control program overall

However, a broader understanding is essential to achieve true control of this disease. TB occurs as a result of a complex and dynamic interplay between the bacillus and humans. The bacillus has an effective strategy of developing resistance to drugs, and an old capacity for latency and opportunism. In healthy people, TB infection is kept in a latent state by effective cell-mediated immunity. The occurrence of TB disease is determined by factors which increase susceptibility; the most important are social and economic factors, so that the poor and the marginalized form the majority of the vulnerable individuals worldwide.

In this chapter, we briefly review the general concepts and currently recommended regimens of TB treatment along with their rationale and limitations. We then discuss some issues and problems in the delivery of treatment, and supportive care with a focus on patients in low- and middle-income countries. In line with the revised End TB Strategy of the WHO (Raviglione 2007), we support the shift from an emphasis on Directly Observed Treatment (DOT, briefly described in Table 8.1) to a patient-centered approach. This approach should be based on an understanding of the social determinants and consequences of TB. Interested readers may wish to also consult evidence-based reviews and recommendations published by WHO (2008, 2010b) and other organizations (Hopewell et al. 2006; World Care Council 2006).

8.2 General Concepts of TB Treatment

8.2.1 Development of Modern TB Chemotherapy Regimens

The discovery of streptomycin for use in TB in 1943 by the team led by Selman Waksman and the trial of 4 months of streptomycin by the Medical Research Council in 1947–1948 laid the foundation for modern TB therapy (Medical Research Council 1948). The results of this trial are still relevant. There was significant clinical improvement with streptomycin in the first 2 months, but resistance developed in 35 of 41 cases with subsequent clinical deterioration; only 8 of 55 patients who received streptomycin became culture negative at 6 months. A later trial used P-aminosalicylic acid (PAS) in combination with streptomycin, with much improved cure rates and no development of streptomycin resistance (Medical Research

Council 1952). A standard 3-drug ("triple") regimen in the 1960s used Isoniazid (INH) and PAS for 18–24 months, with streptomycin for the first 3 months. The prolonged duration of therapy was necessary to prevent relapse after apparent cure. The development of rifampicin and pyrazinamide allowed use of much shorter regimens, with minimal risk of relapse. A series of landmark clinical trials coordinated by the British Medical Research Council (MRC) and conducted in a number of low- and middle-income countries resulted in the formulation of the modern standardized two-phase regimen. This regimen used four drugs [isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E)] in the initial intensive phase of 2 months (2HRZE) and two drugs (isoniazid and rifampicin) in the continuation phase for 4 months (4HR; Fox et al. 1999). This (2HRZE/4HR) is the shortest possible regimen for patients with drug susceptible TB (DS-TB) that can achieve the three basic objectives of TB treatment.

8.2.2 Objectives of TB Treatment

The first objective of TB treatment is to provide immediate individual benefit by improving symptoms, reducing disability, and preventing death. The second objective is to provide immediate public health benefit by reducing contagiousness and preventing further transmission. The third objective is to provide long-term individual and public health benefit by preventing the emergence and transmission of drug resistant TB (DR-TB). As stated in the International Standards of Tuberculosis Care, "any practitioner treating a patient for tuberculosis is assuming an important public health responsibility. To fulfil this responsibility, the practitioner must not only prescribe an appropriate regimen, but also be capable of assessing the adherence of the patient to the regimen and addressing poor adherence when it occurs" (Hopewell et al. 2006).

8.2.3 How Drug Resistance Develops

The rising occurrence of drug resistance in TB now threatens individual cure and effective public health control. The emergence and dissemination of drug resistance is the result of human and societal failures. Many TB programs, especially in low- and middle-income countries, failed to recommend effective TB regimens, did not ensure supervision of patients, and did not maintain an uninterrupted drug supply. Physician errors such as prescribing regimens with inappropriate number or combinations of drugs, or suboptimal dosing and duration, or adding single drugs to failing regimens, plus patient nonadherence have all contributed to development of drug resistance. The types of drug resistance are summarized in Table 8.2. Monodrug resistance and polydrug resistance to INH and other drugs first appeared in the 1950s, while multidrug resistance (MDR, defined as resistance to at least INH and

Table 8.2 Types of drug resistance in TB (WHO 2008)

Resistance	Definition
Monoresistance	resistance to one anti-TB drug
Multidrug resistance (MDR)	resistance to at least isoniazid and rifampicin
Polyresistance	resistance to at least two first-line anti-TB drugs, but not to rifampin
Extensive drug resistance (XDR)	multidrug-resistance plus resistance to any fluoroquinolone and at least one of three injectable second-line drugs (capreomycin, kanamycin, and amikacin)

Rifampin) appeared in the 1980s soon after the introduction of Rifampin. Extensive drug resistance (XDR), defined as MDR plus resistance to a fluoroquinolone plus a second-line injectable drug, was first described in 2004.

8.2.4 Impact of Clinical History and Manifestations on Treatment

Patients with active TB can be classified on the following bases:

- Site of disease: Pulmonary and Extrapulmonary TB.
- Drug susceptibility tests: DS-TB or DR-TB.
- Treatment history: New cases or previously treated cases.

The treatment of pulmonary and extrapulmonary TB is identical, except supplemental corticosteroids, or a longer duration of treatment may be indicated for some forms of extrapulmonary TB like meningeal TB.

The distinction between drug susceptible and drug resistant TB is of immense significance for the selection and duration of anti-TB drugs. DS-TB can be treated with a standard 6-month regimen (see below), while DR-TB requires therapy tailored to the drug resistance profile, and usually involves more drugs given for much longer.

In most low- and middle-income countries, drug susceptibility testing is not available, and patients are classified into two groups based on previous history of treatment, as this correlates with probability of drug resistance. A new patient is someone who has never been treated before, or has been treated for less than 1 month. The great majority of new patients will have DS-TB unless they have developed active TB after contact with a patient with documented DR-TB (WHO 2010b). Patients with previous history of treatment can be categorized into treatment failures (failed during treatment), relapses (recurrence of TB following previous cure) or relapse after failing to complete, or treatment interruptions (a significant interruption is defined as 2 months or more). Previously treated patients have higher prevalence of all types of drug resistance including mono-drug resistance, polydrug resistance, MDR-TB, and XDR-TB (Espinal et al. 2000). In previously treated persons, the probability of any resistance is about four times higher and probability of MDR-TB is ten times higher than in new cases (WHO 2008).

8.3 Treatment for New Patients with Known or Presumed Drug Susceptible TB

8.3.1 New Cases

Regimen: 2HRZE/4HR

This regimen is appropriate for pulmonary TB and all forms of extrapulmonary TB except meningeal TB or bone and joint TB, for which 9 months of therapy is recommended (2HRZE/7HR). Daily dosing is preferable (WHO 2010b). An acceptable alternative is daily dosing during the intensive phase followed by thrice weekly dosing during the continuation phase ($2HRZE/4(HR)_3$). Initial intermittent dosing resulted in higher rates of acquired drug resistance and significantly higher rates of relapse (Menzies et al. 2009).

The British MRC studies on short course chemotherapy provided the evidence base for the regimen (Fox et al. 1999). A regimen of 2SHRZ/4HR (S = Streptomycin) was used in Singapore, with either daily or intermittent dosing in the continuation phase. This regimen resulted in no failures and only 3 % relapse rate after 5 years. This regimen was modified, without supportive evidence from a randomized controlled trial, to use ethambutol instead of streptomycin (2HRZE/4HR) (Mitchison 2004). In one subsequent randomized controlled trial, the 2HRZE/4HR regimen resulted in 3 % failure and 5 % relapses within 12 months after the end of treatment (Jindani et al. 2004). In 6402 patients treated with this regimen under program conditions in six nations, treatment success was seen in 83 %, but 3 % failed and 2 % died (Espinal et al. 2000).

8.3.2 New Cases in Regions with High Prevalence of Isoniazid Resistance but No Drug Susceptibility Testing (DST)

Regimen: 2HRZE/4HRE

The addition of ethambutol throughout the continuation phase is based on expert opinion (WHO 2010b). The precise prevalence at which this recommendation should be implemented is not specified.

8.3.3 New Cases with HIV Coinfection

Regimen: 2HRZE/4–7HR

All patients with TB should receive provider-initiated testing for HIV infection, since the risk of developing TB is 26–31 times higher in persons with HIV infection, compared to people without HIV infection. Since TB can be the first illness in an HIV-positive person, screening for HIV infection in the presence of known or

suspected TB offers opportunities for HIV prevention, care, and treatment. Among persons with active TB, the mortality of HIV-positive persons is greater than in HIV-negative persons (WHO 2010b).

Intermittent thrice a week dosing during the intensive phase is not recommended, as the incidence of failure and relapse was three times higher with intermittent dosing compared to daily therapy (Khan et al. 2010). Additionally, a total duration of therapy of 8–9 months should be considered, since a recent systematic review found lower rates of relapse with 8 or more months of rifampicin containing regimens compared to the standard 6-month regimen (Khan et al. 2010).

All HIV-positive TB patients should receive co-trimoxazole preventive therapy throughout their treatment. Co-trimoxazole reduces mortality in HIV-positive TB patients by preventing *P. jiroveci* pneumonia and bacterial infections.

After TB therapy has been initiated in all HIV-positive TB patients, antiretroviral therapy (ART) should be initiated as soon as possible and within 8 weeks of initiating anti-TB treatment, irrespective of the CD4 cell count. ART should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase inhibitor (NNRTI). The NRTIs recommended include zidovudine (AZT) or tenofovir disoproxil fumarate (TDF) combined with either lamivudine (3TC) or emtricitabine (FTC). In HIV-positive TB patients, the NNRTI efavirenz is preferred because of its minimal interactions with TB drugs (WHO 2010b). Initiating ART early increases survival, improves TB outcomes, reduces incidence of immune reconstitution inflammatory syndrome, and reduces TB transmission.

8.3.4 Limitations of the Standardized Regimen for New Patients

8.3.4.1 Long Duration

Six months of therapy is a very long period of time for a patient to endure. There is currently no regimen that has been found which combines a duration of less than 6 months with a low risk of relapse. There is an urgent need for new more rapidly effective drug regimens that will allow substantial shortening of therapy.

8.3.4.2 Multiplicity of Drugs

TB chemotherapy requires multiple drugs to achieve a durable cure and minimize the risk of emergence of drug resistance. This adds to the cost, toxicity, and complexity, as well as increases the risk of patient nonadherence and/or physician prescription errors. Given a large quantity of pills to take, patients may selectively omit particular medicines; this will increase the risk of emergence of drug resistance. Fixed dose combinations are recommended by the WHO as these will prevent selective drug intake, aid adherence by reducing pill burden, reduce the risk of incorrect dosing, and simplify drug supply management. However, all FDCs should be of

proven bioavailability and in the WHO-recommended strengths, which can be ensured by procurement from WHO prequalified manufacturers. A recent systematic review of 15 randomized trials concluded that these trials did not provide evidence that the use of these formulations improved treatment outcomes in patients with active TB (Albanna et al. 2013).

8.3.4.3 Adverse Reactions to Anti-TB Drugs

The toxicity of anti-TB drugs can be troublesome and occasionally serious. All anti-TB drugs commonly cause nausea, anorexia, and vomiting. Isoniazid, rifampicin, and pyrazinamide can cause liver injury; isoniazid can also cause peripheral neuropathy, while ethambutol can decrease visual acuity.

8.3.4.4 High Costs of Therapy

The patients' costs associated with TB therapy are considerable as they must pay direct costs (of other medicines, consultations, and diagnostic services), and also bear indirect costs of lost wages because of absenteeism, time spent on follow-up visits, travel costs, and wages lost by any accompanying family members. Even when TB care is provided free, patients have often incurred significant direct costs by the time the diagnosis is established, and continue to incur significant costs during treatment. In one study in India, patients lost an average of 83 days of wages and incurred $171 in out-of-pocket expenses. This amounted to 40 % of the total annual income and created a debt equivalent to 14 % of their annual income (Rajeswari et al. 1999). A similar study in Zambia showed that the total cost to patients for diagnosis and 2 months of treatment was 47.8 % of their median monthly income (Aspler et al. 2008). An important finding, in Zambia as well as Brazil, was that clinic-based DOT increased the economic burden on the patients by 2–3 fold in comparison to self-administered treatment (Aspler et al. 2008; Steffen et al. 2010). In the new End TB Strategy, the indirect and direct costs of TB treatment are receiving attention, and it is hoped that no TB affected household will incur catastrophic costs related to TB treatment by 2020. In a cohort study from Peru where patients, including patients with MDR-TB, were offered free treatment, treatment still resulted in impoverishment. Catastrophic costs, defined as costs greater than 20 % of annual household income, correlated with adverse patient outcomes in this study. It was also found that the adjusted population attributable fraction of adverse outcomes explained by catastrophic costs was similar to that explained by MDR-TB (Wingfield et al. 2014).

8.3.4.5 Poor Outcomes if New Cases Have Unsuspected Drug Resistance

The outcomes of treatment with the standard regimen for new cases are worse if patients are infected with any DR-TB strain. Initial resistance to isoniazid is common with a global weighted mean of 7.4 % in new cases (WHO 2010a). In a recent

systematic review, 13 % of patients with initial isoniazid resistance who were given the standard 6-month regimen either relapsed or failed treatment, and many had additional acquisition of resistance to rifampicin resulting in MDR. Outcomes were worse in patients with polydrug resistance. Failure and relapse rates exceed 60 % in patients who received standard therapy for new cases but had underlying MDR-TB (Lew et al. 2008). The new End TB Strategy aims to achieve universal drug susceptibility testing in all patients though establishment of facilities for conducting drug susceptibility tests (rapid and conventional) will be a challenge in low- and middle-income countries.

8.4 Treatment for Patients with Known or Suspected Drug Resistant TB

8.4.1 Standardized Regimen for Previously Treated Patients

Regimen: 2HRZES/1HRZE/5HRE

The WHO has proposed a re-treatment regimen consisting of first-line drugs for use in situations where the probability of MDR-TB in the previously treated group is low or moderate (on the basis of surveillance data). Among previously treated patients, prevalence of DR-TB is lower in those with relapse or prior default from therapy than those who have failed therapy. The overall treatment success rate for the standardized re-treatment regimen globally is 70 %; success rates are even lower in populations with high likelihood of MDR-TB in previously treated patients, such as in the Russian Federation (WHO 2009). Recommended regimens for DR-TB (non-MDR) are listed in Table 8.3.

Table 8.3 Treatment of non-MDR drug resistant TB (WHO 2008)

Drug resistance	Suggested regimen	Minimum duration of treatment
H (±S)	R, Z, E (fluoroquinolone may be considered)	9 months
H and Z	R, E, fluoroquinolone	9–12 months
H and E	R, Z, and fluoroquinolones	9–12 months
R	H, E, fluoroquinolones, plus at least 2 months of Z	12–18 months
R and E (±S)	H, Z, fluoroquinolones, plus an injectable drug for at least 2–3 months	18 months
R and Z	H, E, fluoroquinolones, plus an injectable drug for at least 2–3 months	18 months
H, E, Z (±S)	R, fluoroquinolone, plus an oral second-line, plus an injectable drug for the first 2–3 months	18 months

H isoniazid, *S* streptomycin, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol

Table 8.4 Treatment strategies when MDR-TB is suspected (WHO 2010b)

	Treatment regimen	
DST availability	While awaiting DST results	Once MDR is confirmed
conventional culture-based DST methods	Empiric treatment with standardized MDR regimen	Continue standardized MDR regimen. Change to individualized MDR regimen if and when DST for second-line drugs is available
rapid molecular methods to detect H and R resistance	Await results (no empiric treatment as results available in 1–2 days)	Initiate standardized MDR regimen
		Continue this, or change to individualized MDR regimen, if and when DST for second-line drugs is available

DST drug susceptibility testing, *MDR* multidrug resistant, *H* isoniazid, *R* rifampicin

8.4.2 Treatment of MDR-TB

MDR-TB can be suspected on the basis of epidemiologic clues like residence in an area with high prevalence of MDR-TB, contact with a known patient with MDR-TB, or clinical evidence such as failure of initial or re-treatment. However, *MDR-TB must always be confirmed by drug susceptibility testing*. In settings where rapid molecular-based DST is available, treatment of MDR-TB can be initiated within 1–2 days. However if conventional solid/liquid media are used, DST results will be available only after 1–2 months. In this circumstance, when the clinical suspicion for presence of MDR-TB is high, then empirical MDR-TB treatment may be started while awaiting the DST results (see Table 8.4). DST results for isoniazid, rifampicin, the injectable drugs, and fluoroquinolones are considered reliable. Results are unreliable for many other drugs, so careful interpretation of these results is needed.

8.4.2.1 Choosing Drugs for Treatment of MDR-TB: The Concept of Drug Groups

Recommended regimens for MDR-TB are not based on randomized controlled trials—as there have been none to evaluate treatment of MDR-TB. The wide variation in patterns of drug resistance in patients precludes recommendation of a single regimen for all patients with MDR-TB. The medicines used for treatment of MDR-TB have been categorized into five groups, as shown in Table 8.5 (WHO 2010b). Regimens should be "constructed" using 1–2 drugs from Group 1, one each from Groups 2 and 3, and then as many as needed from Groups 4 and 5 to make sure there are an adequate number of likely effective drugs (Caminero et al. 2010).

Table 8.5 Groups of drugs used to treat MDR-TB (WHO 2014a)

	Drug	Dose (per day unless marked)
Group 1	Pyrazinamide	25 mg/kg
First-line oral anti-TB drugs	Ethambutol	15 mg/kg
Group 2	Kanamycin	15 mg/kg
Injectable drugs	Amikacin	15 mg/kg
	Capreomycin	15 mg/kg
Group 3	Levofloxacin[a]	10–15 mg/kg
Fluoroquinolones	Moxifloxacin[a]	7.5–10 mg/kg (usually 400 mg in adults)
Group 4	Ethionamide/Prothionamide	15 mg/kg
Oral bacteriostatic	Cycloserine/Terizidone	10–15 mg/kg
second-line drugs	Para-amino-salicylicAcid (PAS)	150 mg/kg
Group 5	Bedaquiline	400 mg once daily for 2 weeks then 200 mg 3 times per week for 22 weeks
Anti-TB drugs with limited data on efficacy and/or long-term safety in treatment of drug resistant TB (including new drugs)	Delamanid	100 mg 12 h
	Linezolid	600 mg
	Clofazimine	100–200 mg
	Amoxicillin/clavulanate	875/125 mg every 12 h
	High dose Isoniazid	10–15 mg/kg
	Imipenem/cilastatin[b]	500–1000 mg IV 6 h
	Meropenem[b]	1 g IV 8 h
	Macrolides (Clarithromycin)	500 mg/12 h
	Thiacetazone	150 mg

[a]These are considered later generation fluoroquinolones and are preferred
[b]These are given in combination with oral clavulanate

8.4.2.2 Principles to Construct an Effective Regimen for MDR-TB

Initial treatment should consist of at least four drugs which are of certain, or nearly certain effectiveness. Factors which suggest that a drug is likely to be effective are: (1) susceptibility on DST, (2) the drug has not been used before, and (3) in prior drug resistance surveys the prevalence of resistance to that drug is low in similar patients. A drug may be included in the regimen even if one is uncertain that it will be effective, but this should not be counted as likely effective.

The drugs should be selected from Group 1 to Group 5. All drugs from Group 1 which are likely to be effective should be used. Only one injectable drug (Group 2) or a later generation fluoroquinolone like levofloxacin or moxifloxacin (Group 3) should be given. Among the injectable drugs, kanamycin is preferable to amikacin and capreomycin. The number of drugs used from Group 4 depends on the number

of drugs needed to constitute an effective regimen. Among the Group 4 drugs, ethionamide is considered the most effective (Ahuja et al. 2012). Drugs in Group 5 are of uncertain efficacy and should be used only if the more active drugs from Groups 1 through 4 cannot be used because of extensive resistance or patient intolerance.

The potential for cross-resistance between drugs should be considered. For example, there is cross-resistance between Kanamycin and Amikacin, among all the fluoroquinolones, and also (in about one third of cases) between Isoniazid and Ethionamide.

All doses of all drugs should be given under direct observation. All second-line drugs should be of assured quality. Drug-related adverse effects should be identified and treated promptly.

The patient should undergo monthly sputum cultures initially. The duration of treatment may be empiric or determined by the time taken to convert to culture negativity (two consecutive negative sputum cultures). Treatment with the injectable drug should be continued for at least 8 months (Falzon et al. 2011). The continuation phase should consist of at least three drugs likely to be effective. The total duration of therapy is at least 20 months in those patients who have not received previous treatment for MDR-TB.

Adjuncts to treatment include surgery and nutritional and social support. Resection surgery can be offered when the patient remains smear positive, has high level resistance to drugs, has localized disease, and when a skilled team for surgical and postoperative care is available (WHO 2008). Nutritional support is critical to prevent a vicious cycle of worsening malnutrition and disease (WHO 2008). Patients with MDR-TB should be provided a range of enablers and incentives that may help maintain adherence to this long and difficult treatment.

In recent years two drugs—bedaquiline (a novel diarylquinoline) and delamanid (a nitroimidazole)—have received approval from drug regulatory authorities in 2012 and 2014, respectively, for their use in MDR-TB. The WHO has issued interim policy guidance on the (compassionate or restricted) use of these drugs as adjunct to optimized background regimens designed according to WHO recommendations in carefully selected patients under controlled settings after obtaining informed consent of patients (WHO 2013b). Bedaquiline has been shown to improve culture conversion, although data on clinical failure or relapse is awaited (Fox and Menzies 2013). Delamanid has been shown to improve mortality and outcomes in patients with MDR-TB (Skripconoka et al. 2013). The use of both these drugs has been associated with QT prolongation, which raises concerns on their use with other second-line drugs like moxifloxacin, or clofazimine which can increase the QT interval. Bedaquiline in addition has been associated with hepatic dysfunction (Fox and Menzies 2013).

8.4.2.3 Limitations of Treatment of MDR-TB

The limitations of the treatment of DS-TB are amplified in the treatment of MDR-TB. The duration of treatment, which may extend to 24 months, is four times longer than for DS-TB. This inflates costs of treatment and the difficulties in

maintaining adherence. Regimens may involve up to seven drugs, especially before obtaining DST results, when the effectiveness of drugs is uncertain, or the resistance or the disease is extensive. Second-line TB drugs cause more side effects, which may be serious and reduce treatment adherence. The costs of treating MDR-TB are 50–200 times higher than treating DS-TB (WHO 2010a). The cost of the drugs required to treat one MDR-TB patient for 24 months exceeds $2100, even when procured at reduced price through the Global Drug Facility. Health system costs are an additional $5000. As a result of these problems, the overall cure rate in the recent 2011 cohort of 52,000 patients with MDR-TB, in the 2014 WHO report, is 48 % (median 59.5 %) and 25 % were lost to follow-up or had no outcome information. Death rates were as high as 21 % in some regions (WHO 2014b).

8.4.3 Treatment of XDR-TB

The principles of treatment of XDR-TB are similar to those in MDR-TB. Hence treatment has the same limitations—prolonged duration, high costs, multiple medications, and frequent side effects. In a meta-analysis, the cure rate in XDR was 44 % (Jacobson et al. 2010), although the global treatment success rates in operational conditions were as low as 22 % (WHO 2014b). The available data on treatment outcomes is derived from observational studies and these principles based on expert consensus have been enumerated in a recent WHO publication (WHO 2014a).

Any drug from Group 1 that may be effective should be used (usually pyrazinamide), but should not be counted as one of the four likely effective drugs. High dose INH may be used if there is low level resistance or absence of katG gene mutation, as this improved rates of sputum conversion in a randomized controlled trial (Katiyar et al. 2008). If there is resistance to aminoglycosides, capreomycin should be used. The administration of an injectable drug for 12 months or throughout the course of treatment should be considered. All Group 4 drugs which have not been used earlier and two or more drugs from Group 5 should be used (Caminero et al. 2010). The use of bedaquiline may be considered as per WHO interim policy guidance. At least six active drugs should be used in the treatment of XDR-TB initially and at least four should be used in the continuation phase (Falzon et al. 2012).

- Surgery should be considered for patients with localized disease.
- Patients should receive full adherence support and close monitoring.
- A recent systematic review showed improvement of treatment outcomes in XDR-TB with use of a later generation fluoroquinolone (moxifloxacin, levofloxacin) even when the DST showed resistance to the representative fluoroquinolone (usually ofloxacin; Jacobson et al. 2010).
- Respiratory infection control measures should be ensured at the site of treatment of the patient. Hospital-based treatment should be considered if the clinical status is poor or if significant comorbidities exist.

8.5 Issues in the Organization and Delivery of Treatment

8.5.1 From Directly Observed Treatment (DOT) to Patient-Centered Treatment

Cure of a patient with TB is most likely when an effective regimen is prescribed and the patient adheres to it. Adherence to treatment is a complex phenomenon which is affected by the organization of TB care services, quality of provider–patient interactions, and patient characteristics. The revised End TB Strategy of the WHO aims to "achieve universal access to high quality diagnosis and patient-centered treatment, reducing human suffering and socioeconomic burden associated with tuberculosis" (Raviglione and Uplekar 2006).

Directly observed therapy (DOT) was used as an alternative to self-administered therapy in some urban programs (e.g., Denver, Hong Kong) in the 1970s and 1980s to ensure adherence. However DOT was not widely implemented because it was unfeasible as well as costly for patients and programs. DOT was used successfully, along with other measures, in New York to improve the low treatment completion rates and help stem the epidemic of TB and MDR-TB in the 1990s (Frieden et al. 1995). The WHO later recommended the universal use of DOT as part of its DOTS strategy, claiming that the intervention was the key to improving treatment completion and preventing the emergence of drug resistance.

The term DOT encompasses a diversity of interventions, as seen in Table 8.6. Reviews of observational studies reporting the beneficial effects of DOT found that co-interventions like incentives, defaulter actions, and patient-centered interventions, rather than DOT alone, contributed to treatment adherence (Volmink et al. 2000). The WHO stated that "implementation of DOT alone with no other supportive measures is unlikely to be effective in promoting adherence" (Maher et al. 2000). A systematic review of six trials comparing DOT to self-administered treatment found no evidence of improved treatment outcomes with the use of DOT (Volmink and Garner 2007).

Clinic (or health facility) based DOT is very demanding on patients as it involves daily or thrice weekly visits. Loss of wages plus travel costs may double the cost of therapy for the patients. Adherence to DOT would be facilitated if community-based DOT was applied. Current evidence and consensus is in favor of a patient-centered approach to treatment where DOT is applied in "a context specific and patient friendly manner" (WHO 2010b). A review of programmatic results showed that treatment success was highest when DOT was accompanied by provision of social support, enablers (e.g., transportation vouchers, convenient clinic timings), and/or incentives (food support, limited financial support) (Chaulk and Kazandjian 1998; see Table 8.6).

Table 8.6 DOT strategies and related terminologies

Classification of DOT	Basis of classification	Comment
Health worker based vs. Layperson or Family based	Person who supervises drug intake	In family-based DOT, a family member observes drug intake. A Cochrane review (Volmink and Garner 2007) observed no difference with health worker-based DOT
Clinic based vs. Community based	Setting for DOT	Clinic-based DOT has been shown to double the indirect costs for patients (Aspler et al. 2008; Steffen et al. 2010)
Universal vs. Selective	Application of DOT to all or selected patients	In many developed countries, DOT is used selectively in those patients who interrupt therapy or are judged likely to have problems in adherence
Fully supervised vs. Modified	Duration of the treatment for which DOT is applied	In modified DOT, all doses in the intensive phase and some in the continuation phase are supervised
DOT vs. enhanced DOT	Use of DOT alone or combined with other measures to promote adherence	Enhanced DOT (DOT + social support + enablers + incentives) has been shown to have the best rate of adherence (Chaulk and Kazandjian 1998)

8.5.2 Reducing Suffering and Socioeconomic Burden Under the End TB Strategy

TB has been termed "poverty's penalty." The poor have a fourfold higher prevalence of infection, and sevenfold higher rate of disease and death (WHO 2005). Long-term debts are incurred, household assets including land are sold, and children drop out of school, with grievous long-term impacts. It is important that TB programs scrutinize the direct and indirect costs incurred by poor patients, adapt their treatment services to minimize them, and offer support wherever feasible.

Baseline hunger is a problem that the poor commonly face. A combination of food insecurity and TB-induced wasting can result in severe undernutrition in poor patients with TB with or without coexisting HIV infection (Tuberculosis Chemotherapy Centre 1959; Zachariah et al. 2002; Van Lettow et al. 2004; Swaminathan et al. 2008). In a large cohort of adult patients with pulmonary TB in rural India, the median weights/BMI were as low as 42 kg/16.0 kg/m^2 in men and 34 kg/15.0 kg/m^2 in women (Bhargava et al. 2013). Undernutrition is a risk factor for death (Zachariah et al. 2002), relapse (Khan et al. 2006), and drug toxicity (Pande et al. 1996). Hence nutritional supplements have been recommended for patients with DR-TB (WHO 2008) and HIV (Huis in 't Veld et al. 2010). We believe, on scientific and ethical grounds, that food insecure patients who are HIV negative or have DS-TB should also receive nutritional supplements. When caloric intake has been supplemented, there have been consistent improvements in weight gain, muscle strength, and shortened time to sputum conversion (Tuberculosis Chemotherapy

Centre 1959; Paton et al. 2004). These improvements can confer socioeconomic benefits through improvements in functional status (Abba et al. 2008). In a recent guideline, the WHO (2013c) has suggested that in view of the "clear bidirectional causal link between undernutrition and active TB, nutrition screening, assessment, and management are integral components of TB treatment and care."

8.6 Areas of Need

If increased access to treatment is to result in reduced transmission and achieve major public health impact, it must be accompanied by increased case-finding. This can be achieved by improving the primary health care network of the public health system by engaging other providers who are preferred by patients and by making TB services accessible to poor populations in both rural and urban areas.

To minimize the adverse impact of TB, DOTS programs need to evolve from a DOT-centered to a patient-centered approach. An equity perspective is also required. The lack of access to public health care services, high costs of care in the private sector, and high indirect costs in clinic-based DOT programs add to the problems of poor patients. TB control programs must be pro-poor in their philosophy, orientation, and practice. This will require flexibility, modification of services, change in provider attitudes, and provision of support.

HIV coinfected patients urgently require better treatment regimens. There is also an urgent need for new anti-TB drugs in this era of MDR-TB and XDR-TB, and for clinical trials to determine the optimal regimens for DR-TB. Finally, we need new TB drugs that will allow patients with drug sensitive TB to complete therapy within 2 months with nontoxic, easily tolerated chemotherapy.

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Chapter 9
DOT Status and Development in China

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9.1 The History of Tuberculosis Chemotherapy in China

Before the advent of effective anti-tuberculosis (TB) drugs in the late 1940s, the main components of treatment involved rest and increasing nutrition. In the early years of chemotherapy, drugs were administered in the hospital. In the 1960s, the implementation of long-term (12–18 month) standard chemotherapy treatment in China resulted in many patients being unable to pay the costs of such long-term hospitalization. Most patients had to be discharged and treated as outpatients late in the course of their treatment, leading to therapy management problems. Adherence to an outpatient treatment protocol depends on patient conscientiousness such as whether or not the patient takes his or her medication as prescribed. It is difficult for patients to adhere to such long-term treatments, so the treatments were ineffective and the cure rate was low.

In 1977, Lixing Zhang of the Institute of Tuberculosis Control of Beijing surveyed two counties in Beijing and discovered that only 55.4 % of new smear-positive TB patients adhered to their medication schedule for 6 months, and only 38.3 % adhered for 12 months (Zhang et al. 1980). The probability of these patients becoming sputum negative in 1 year was only 44.1 %. The main reason for these poor results was due to lack of treatment adherence.

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Fifty years ago, United States TB control experts first proposed that TB patients should be supervised while taking medication in order to ensure that TB treatment is completed. This principle of Directly Observed Therapy (DOT) was widely applied in Hong Kong and Madras, India.

9.1.1 DOT Is Brought to Treatment Management of TB Patients

In the 1980s, directly observed treatment, short-course (DOTS) began to be promoted in China; the treatment time of infectious cases was shortened to 6 months (for new cases) to 8 months (for re-treatment cases) and long-term isolation of patients was no longer needed. The management of TB patients continued outside the hospital. Special outpatient TB treatment programs were set up in the cities of Beijing and Shanghai.

9.1.1.1 The Fully Supervised TB Management Program in Beijing

In the early 1960s, the Beijing Research Institute for Tuberculosis Control and Epidemiology and the Beijing Tuberculosis Research Institute cooperated in a study of the intensive stage of chemotherapy in TB outpatients. At the end of 6 months, 96.1 % of the patients had completed treatment and 83.2 % had been cured (Li et al. 1965).

In 1978, Professor Lixing Zhang of the Beijing TB Control Institute studied nonhospitalized TB patients in rural areas who received overall supervision for their chemotherapy (Zhang et al. 1980). He studied fully supervised chemotherapy implementation in new nonhospitalized TB patients who were taking intermittent chemotherapy (three times per week) in two counties in Beijing. The pilot study was designed to test the suitability, feasibility, acceptability, and effectiveness of DOT in the full course of treatment. After diagnosis, professional medical staff educated the patient on the characteristics of TB and the advantages of DOT. Any issues the patient had with using DOT were resolved where possible. The professional medical staff then contacted the patient's primary healthcare or community healthcare workers, explained the situation, and established "three fixed," where the medication time, location, and observing supervisor were all fixed in order to encourage compliance. The medical staff talked to the patient before drugs were taken so any problems could be identified and resolved immediately. The TB patients obtained their drugs at TB dispensaries and gave them to the primary healthcare workers when they began DOT. Supervisors directly observed each dose. Staff witnessed and recorded when the drugs were taken. To ensure that patients regularly took their medication, refills were supplied within 24 h. If patients didn't take anti-TB drug according to treatment regimen, medical personnel would take remedial measures such as home visits or telephone inquiries. If the local community healthcare system was not perfect, or it was geographically spread out and/or it was difficult for medical personnel to reach

the patient, then family members could be trained to act as supervisors. Family members who were serious, responsible, and had a certain education background were preferentially selected. These persons were trained by professionals and had to pass an exam to be supervisors. The pilot study showed that this program was acceptable, practical, and feasible for achieving high treatment completion rates (99.6 %) and sputum conversion rates (98.6 %). The conversion rate for the smear-positive pulmonary TB (PTB) patients treated for 12 months was defined as the percentage of patients who had negative results in the 10-month, 11-month, and 12-month follow-up smear sputum examination. For patients who received treatment less than 1 year, it was defined as the percentage of patients who had negative results for three successive follow-up smear sputum examinations (Zhang et al. 1980).

Beginning in 1979, this form of fully supervised and nonhospitalized intermittent chemotherapy was gradually implemented in 18 districts and counties in Beijing as the standard treatment. Newly diagnosed, smear-positive, untreated TB cases were prime targets for fully supervised chemotherapy. These cases were diagnosed by sputum examination criteria. Patients with economic difficulties were offered subsidized drugs. Due to better implementation of fully supervised chemotherapy for new smear-positive cases, especially in rural areas, this practice was adapted for patients requiring re-treatment as well. Fully supervised re-treatment was slowly adopted as a routine procedure.

The prevalence of TB was markedly reduced in Beijing. The national TB epidemiological survey showed that the prevalence of smear-positive TB cases in Beijing decreased from 127 per 10 million in 1979 to 56 per 10 million in 1985 and was further reduced to 16 per 10 million in 1990. This represents an average reduction of 17 % per annum (Zhang 1997). By 1992, the DOT coverage rate reached 98 %, the sputum-negative conversion rate was more than 95 %, the cure rate for first-time infections was 94 %, and the treatment failure rate was only 2.5 % (Wang et al. 2004) (Table 9.1).

After the implementation of DOT, the drug adherence rate in TB patients increased from 40 % in 1978 to more than 95 % in 1990. This significantly reduced treatment withdrawal and irregular treatment rates. DOT increased the treatment success rate from about 50 to 90 %, and reduced the failure rate and loss of contact rate to <5 % (see Table 9.2). The recurrence rate dropped from 10 % to generally less than 5 % with some variance across regions (Wang et al. 2004).

The TB epidemic in Beijing decreased dramatically based on national TB epidemiological surveys in 1979, 1985, and 1990; the prevalence of smear-positive TB was 127/100,000, 56/100,000, and 16/100,000, respectively, with an annual decrease of 17 %. As the TB epidemic in Beijing dropped to the lowest level across the country, this success attracted attention home and abroad.

9.1.1.2 The Whole Course Management Chemotherapy Program in Shanghai

As DOT was implemented in Beijing, Shanghai was exploring another management model: whole course management chemotherapy (Yan and Duanmu 2003). This program was implemented as follows: once patients were diagnosed with PTB in

Table 9.1 DOT coverage of new smear-positive cases in Beijing from 1978 to 1996 (Wang et al. 2004)

Year	DOT coverage	DOT completion rate
1978	10	nd
1979	30	nd
1980	45	nd
1981	62	nd
1982	76	nd
1983	75	nd
1984	81	92
1985	63	92
1986	70	89
1987	78	90
1988	87	87
1989	87	88
1990	93	92
1991	97	95
1992	98	96
1993	98	96
1994	97	94
1995	96	91
1996	91	90

nd no data

Table 9.2 Cohort analysis of newly recorded infections in Beijing from 1985 to 2001 (Wang et al. 2004)

Year	Total cases	Cured (%)	Still positive (%)	Deaths (%)	Moved (%)	Lost contact (%)
1985	1945	1661 (85.4)	86 (4.4)	66 (3.4)	25 (1.3)	107 (5.5)
1987	1808	1625 (89.9)	99 (5.5)	54 (3.0)	16 (0.9)	13 (0.7)
1989	1210	1089 (90.0)	53 (4.4)	39 (3.2)	11 (0.9)	18 (1.5)
1991	1219	1147 (94.1)	31 (2.5)	33 (2.7)	5 (0.4)	2 (0.2)
1993	764	732 (95.8)	5 (0.7)	18 (2.5)	2 (0.3)	6 (0.8)
1995	819	745 (91.0)	6 (0.7)	38 (4.6)	12 (1.5)	18 (2.2)
1996	778	723 (92.9)	9 (1.2)	33 (4.2)	8 (1.0)	5 (0.6)
1997	786	709 (90.2)	31 (3.9)	33 (4.2)	4 (0.5)	9 (1.1)
1998	802	721 (89.9)	23 (2.9)	46 (5.7)	5 (0.6)	7 (0.9)
1999	764	703 (92.0)	22 (2.9)	32 (4.2)	0 (0.0)	7 (0.9)
2000	733	672 (91.7)	28 (3.8)	20 (2.7)	6 (0.8)	7 (1.0)
2001	660	618 (93.6)	7 (1.1)	22 (3.3)	7 (1.1)	6 (0.9)

county-level TB dispensaries, they would receive health education before chemotherapy. Then they would start one of two treatment regimens: a 12–18 month treatment with isoniazid (H), streptomycin (S), and para-aminosalicylic acid (PAS) or a 6–8 month treatment with H, rifampicin (R), pyrazinamide (Z), and either streptomycin (S) or ethambutol hydrochloride (E). TB patients obtained drugs from TB

dispensaries, took drugs independently, and returned for follow-up and smear tests. Patients picked up drugs every 2 weeks or once a month in the intensive phase and once per month in continuation phase. Health workers in TB dispensaries regularly visited patients at home, checked the patient's inventory of medications, and observed the color of patient urine (to confirm the metabolism of rifampicin). If a patient missed a drug pickup at the TB dispensary, health workers would trace patients within 3–5 days in order to guarantee adherence to treatment.

In the 1990s, Shanghai developed a whole management protocol which included a family member as a supervisor. Family member supervisors were selected by the village doctor from parents, children over 15 years old, or other relatives, and must have met certain education requirements. Family supervisors were responsible for participating in initial education and training from health workers, knowing the medications (compound, dosage, storage, and possible adverse reactions), keeping the drugs, watching the patient swallow each dose, filling out the treatment card, and urging patients to get their refill drugs from TB dispensaries and get their follow-up smear tests. This whole course management obtained good chemotherapy results through good compliance. Shanghai achieved substantial progress in TB control since the 1970s by implementing the whole management program. The third national TB epidemiological survey in 1990 indicated that TB epidemic decreased dramatically and decrease rate ranked second among 30 provinces (Ministry of Health of The People's Republic of China 1992).

In 1992, the National Center for TB Control and Prevention and the TB Research Institute in Zhejiang province compared the impact of whole course management with DOT on newly diagnosed smear-positive TB patients treated with $2H_3R_3Z_3E_3/4H_3R_3$ (Yan and Duanmu 2003). Results revealed that rates of interrupted treatment were 0.12 % for patients with whole course management and 0.16 % for patients with DOT, and the conversion rates were 98.9 % and 96.9 %, respectively ($p > 0.05$). This indicated that whole course management can be as effective as DOT (Dai et al. 1994).

9.1.2 Application and Development of DOT Strategies

Based on the success of the fully supervised chemotherapy program in Beijing, other regions in China began to pursue the nonhospitalized, fully supervised approach to TB chemotherapy. Programs across the country obtained consistently positive results, and DOT was considered best practice for controlling TB. Nevertheless, DOT was not universally implemented and TB control results differed greatly across the country. An epidemiological survey in 1990 showed that except for Beijing, Shanghai, and a few other cities with rapidly declining TB rates, about half of the provinces in the country had only a slight drop in TB rates, and the epidemic in some provinces had not decreased or was increasing. To address this situation, the government increased domestic investment in TB control efforts and attracted foreign investment to implement TB control programs. The Chinese government promoted modern TB control strategies such as DOTS (Ministry of Health of The People's Republic of China 1992).

9.1.2.1 The Application of DOT Policy in TB Control Program

The Chinese government used World Bank loans for a TB control project (the Health V Project) from 1992 to 1998. The Health V Project was conducted in 13 provinces, municipalities, and autonomous regions. From 1992 to 1998, the Ministry of Health used Chinese government financing to implement the Strengthen and Promotion of Tuberculosis Control Project in 15 provinces. Both of these projects made DOT the core content of the DOTS throughout the full implementation and application of the projects. Anti-TB drugs were provided for free by the government, mainly to those patients with untreated smear-positive pulmonary TB, retreated smear-positive TB, and smear-negative patients with severe symptoms. In principle, smear-positive patients were required to implement DOT, and smear-negative patients who qualified for free medication were required to implement the whole course administration of chemotherapy as modeled in Shanghai.

Protocols of DOT Implementation

Under these two projects, once patients were diagnosed, the village doctor took custody of the anti-TB drugs and the patients were required to make regular visits to the health center or village doctor for dosing. After each dose or injection the doctors were required to make a record of treatment on a registration card. If a patient failed to take medication, the doctor was required to take remedial measures within 24 h. This could include a home visit to determine the reason for missing treatment, a reminder to the patient of the importance of being treated regularly, and the provision of the missed medication or injection. As required by the DOT program, the medical staff was required to summarize this process as "drug delivered at home, witnessed medicine being taken, recorded dosing before departure, if failed remedy in a timely fashion." In this way, patients were compelled to adhere to an uninterrupted treatment protocol so as to achieve a higher cure rate and a lower rate of relapse. Since DOT was predominantly implemented by rural doctors, these programs required rural doctors to be trained by provincial, city, and county doctors, and also required that they receive regular supervision. In addition, the programs prescribed for supervisory doctors to be rewarded when patients were cured (Cai and Chen 2003).

Developed Combinations of Anti-TB Drugs

The Health V Project adopted the intermittent chemotherapy scheme; untreated smear-positive patients were treated with $2H_3R_3Z_3S_3/4H_3R_3$ or $2H_3R_3Z_3E_3/4H_3R_3$. This reduces by half the number of whole course medications, which is convenient for the patient and also reduces the number of supervisions required by the medical staff. In order to ensure that patients get the correct medications at the proper doses, the various anti-TB drugs are packaged into a variety of combination packs

according to the particular chemotherapy regimen. This combination packaging supply system is suited to China's pharmaceutical industry and is quite popular with patients. The patients simply have to take one package every other day.

Project Cure Rates

The average cure rates of TB in both project areas met the World Health Organization (WHO) target (85 % by the year 2000). In the Strengthen and Promotion of Tuberculosis Control Project, the average cure rate for newly diagnosed smear-positive TB cases was 93.3 % (Zhong and Tang 2013). In the Health V Project provinces, the average cure rate for newly diagnosed smear-positive TB cases was 95.6 % and the cure rate for retreated smear-positive patients was 90.4 % (Cai and Chen 2003).

9.1.2.2 Promotion and Development of the DOT Strategy in TB Control Program

China carried out The Third National TB Prevalence and Control Plan from 2001 to 2010. In order to promote the plan, a new capital raising mechanism was devised by the World Bank and supported by the United Kingdom's Department for International Development (DFID) and the Chinese Government. In 2002, through a World Bank loan and a DFID grant, China implemented the Health X Project in 1450 districts in 188 cities across 16 provinces. This was the biggest TB control project in the world. The Health X project was expanded and improved based on experiences from the Health V Project. The DOTS strategy was fully implemented in all 16 provinces, and DOT implementation and administration was more standardized. The scale of free diagnosis and treatment was expanded to include new smear-positive patients, new smear-negative patients with cavity or miliary TB (since 2006, all new smear-negative cases were expanded), and retreated smear-positive patients in recurrent populations. Migrant TB patients were included in local DOT. More attention was paid to the implementation of chemotherapy under supervision. In places where it was difficult to implement DOT, such as in inaccessible remote mountainous and pastoral areas or large areas with scattered populations, the patient's family members or other personnel were trained to monitor the taking of medication by the patient. The project also offered some travel allowance to TB patients who lived far from their doctors, so they could obtain their medicine on time and avoid interruption of treatment.

Since 2002, several other internationally funded TB control projects have been undertaken in China. These include the Belgian Damien Foundation TB Control Project, the Canadian International Development Agency's TB Control Program (developed in collaboration with the WHO), and the Global Foundation TB Control Project. These projects, which are being conducted according to DOT policy, are laying the foundation for achieving the WHO goals for TB treatment in China set in 2005 (Zhang and Wang 2010).

9.1.3 DOT Strategic Planning

The purpose of managed treatment is to reduce the number of infectious TB patients. This is accomplished by increasing negative sputum conversion rates through persistent regular treatment so as to eliminate infections and cut off the transmission of TB. Managed treatment of TB patients is key to the success of chemotherapy and is currently the primary means of controlling the TB epidemic. Consequently, fully supervised chemotherapy DOT is one of the mainstays of China's National Tuberculosis Control Program.

9.1.3.1 National Tuberculosis Control Program 1981–1990: Implementation of the Non-hospitalization Chemotherapy Policy and Adoption of Fully Supervised Treatment Measures

The Ministry of Health implemented the first Ten Year Plan for TB control from 1981 to 1990. The main objective of the plan was to reach untreated patients and thereby reduce the number of sputum smear-positive infectious individuals. Non-hospitalization chemotherapy was strongly recommended. The existing program in Beijing (see Sect. 9.1.1.1) was incorporated, and another form of practical treatment and management was developed in Shanghai (see Sect. 9.1.1.2). Under the plan, treatment and management of smear-positive patients increased, and newly diagnosed smear-positive patients treated with short-course chemotherapy increased by 80 %. Though short-course chemotherapy programs were strongly promoted, only 24 % of the registered smear-positive patients were treated and managed in accordance with the DOT method. The cure rate for smear-positive patients rose from 59.9 % in 1986 to 76.4 % in 1990 (Yan and Duanmu 2003).

By 1990, the nationwide prevalence of TB had been reduced by 30–50 % when compared to an epidemiological survey taken in 1979. The adherence rate of smear-positive patients who had taken medicine in the prevention of institutional management reached 90 %. By the end of the Ten Year Plan, the sputum conversion rate reached 80 % in rural areas and more than 90 % in urban areas. Although significant progress had been made in several important areas, the 1981–1990 Ten Year Plan fell short of achieving all of its goals.

9.1.3.2 National Tuberculosis Control Program 1991–2000: Full Implementation of DOT as the Key to DOTS

The goals of the 1991–2000 Ten Year Plan included a treatment coverage rate of 95 % for newly diagnosed smear-positive TB patients, a treatment completion rate of 85 %, and a sputum conversion rate of 90 %. In order to achieve these goals, China implemented the Health V Project and the Strengthen and Promote TB Control Project (see Sect. 9.1.2). These programs fully implemented DOT as the core component of DOTS in the project areas, and in the majority of the study areas DOT was

implemented by trained healthcare workers. During this period, 1.46 million infectious TB patients were diagnosed and treated for free in the project area, and the cure rate rose from 50 to 90 % (Yan and Duanmu 2003).

9.1.3.3 National Tuberculosis Control Program 2001–2010: Continuing to Improve Effective Implementation of DOTS and DOT

In order to consolidate previous achievements and improve three areas of difficulty in fully and effectively implementing modern TB control strategies, the 2001–2010 Ten Year Plan put forward the following targets: 95 % of counties covered with DOTS strategy, 85 % of infectious TB patients receive fully supervised treatment, and an 85 % cure rate. Therefore, this Ten Year Plan required immediate and supervised treatment of TB patients. All cases were required to be reported, registered, and treated without delay. Because the 4th National Epidemiological Survey conducted in 2000 showed that the TB epidemic was more severe in rural areas, and that 80 % of TB patients lived in rural areas, the main focus of the 2001–2010 Ten Year Plan was on the countryside. In order to ensure compliance and effectiveness, the Ministry of Health's Disease Control Division developed a *China Tuberculosis Control Program Implementation Guide* in 2002. The guide outlined in greater detail the provisions and requirements for managing patients with pulmonary TB with emphasis on the implementation of DOT. The guidelines required that all smear-positive TB patients receive fully supervised chemotherapy directly observed by the medical staff. It also required that the DOT strategy be implemented on three levels: county, town, and village. Doctors and medical staff at all three levels take responsibility for treatment. The guide emphasized the role of town and village doctors in the supervision and management of treatment, including aspects such as record keeping, observation and management of adverse drug reactions, urging patients to periodically review their progress, adopting various forms of publicity, and ensuring adequate drug supplies. It also defined management structures and procedures.

The mid-term evaluation report of the 2001–2010 Ten Year Plan showed that from 2002 to 2005, the average rate of implementation of DOT in all registered smear-positive patients was 87.2 %. Of the remaining patients, 9.5 % used DOT during the intensive phase of chemotherapy and the whole course management method during the continuation phase, 2.9 % implemented the whole course management, 0.2 % took medication independently, and 0.2 % refused medical treatment (see Fig. 9.1.) The annual rates of fully supervised chemotherapy over the 4 years from 2002 to 2005 were 53, 88, 91, and 93 %, demonstrating the improving quality of managed treatment year by year (Xiao and Wang 2008).

The *China Tuberculosis Control Program Implementation Guide* was revised to adapt DOT more appropriately in China and incorporate new data. The revised version was issued in 2008. The guide adapted the DOT for smear-positive PTB patients and newly diagnosed smear-negative patients with cavity or miliary PTB. Patient chemotherapy would be supervised during the whole treatment course by health workers, family member, or volunteers. Supervisors may include:

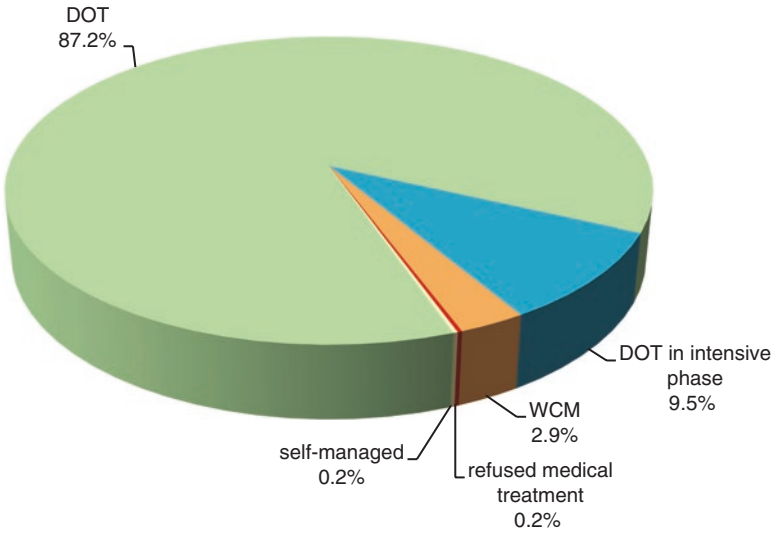

Fig. 9.1 Mid-term evaluation of the 2001–2010 Ten Year Plan (Xiao and Wang 2008). Chemotherapy supervision for registered smear-positive PTB patients between 2002 and 2005. Patients using DOT in the intensive phase only followed WCM in the continuation phase of chemotherapy. *DOT* directly observed therapy, *WCM* whole course management

1. Medical staff: people who work for Chinese Center for Disease Control and Prevention (China CDC) branches, health clinics in towns and townships, or Community Service Centers
2. Family members: a parent, child, or spouse living with the TB patient who is older than 15, has graduated from primary school, and is trained by a professional with knowledge of how to supervise the patient and fill out treatment reports
3. Volunteers: anyone other than medical staff or patient family member who is older than 18, has graduated from junior middle school, and is trained by a professional with knowledge of how to supervise the patient and fill out treatment reports

The following rules apply to supervision: supervision management of patient treatment should be carried out by medical staff unless the distance between the patient's house and the community service center is more than 1.5 km, or unless the country doctor cannot afford to take the responsibility. In those cases, family members or volunteers can take charge of supervision. Patients accepting multidrug-resistant TB (MDR-TB) treatment programs must be supervised by medical staff.

The responsibilities of the supervisor are indicated clearly:

1. The time and place of medication should be set according to the patient's situation and DOT should be applied.
2. If the patient does not take the medicine on time, remedial measures should be taken immediately.

3. The record card should be filled soon after the medication is taken.
4. If an adverse reaction to medication occurs or the patient does not take the medication on time, it should be reported to the physician supervisor immediately and response measures should be taken.
5. Patients should be supervised and urged to do periodic follow-up and assist in collecting sputum specimens.
6. After the whole course of treatment is completed, urge the patient to deliver their treatment records to the county district TB control institution for archiving (Ministry of Health et al. 2009).

These updated guidelines are more suited for DOT implementation in rural areas.

9.2 Challenges for DOT Performance in China

9.2.1 Problems

According to the *China Tuberculosis Control Program Implementation Guide* (2008), supervision of smear-positive TB patients should be carried out during the entire course of chemotherapy. Based on the report issued by National Center for TB Control and Prevention of the China CDC, 90 % of smear-positive TB patients received their entire treatment under the DOT system, about 8 % began treatment under the DOT system sometime during the intensive phase of chemotherapy, and about 2 % of patients did not receive DOT treatment (Tu et al. 2013). However, according to the on-site supervision and domestic researchers' reports, the enrollment rate of DOT in some areas was lower, especially in those poverty-stricken areas that lack healthcare facilities. In September 2000, an assessment group formed by the WHO and the Chinese Anti-Tuberculosis Association launched a site assessment in China. Four provinces were randomly selected, and 40 patients from each of 4 counties from each province took part in the investigation. In this assessment, 64.7 % of smear-positive TB patients received chemotherapy under DOT guidelines during the whole course of treatment and an additional 7 % enrolled in DOT during the intensive phase of treatment only, for a total rate 71.7 % (Fig. 9.2; Cai and Chen 2003).

The World Bank DFID China TB Control Project 2004, which was carried out in Liaoning, Fujian, He'nan, and Xinjiang provinces, reported that only 57.2 % of the patients received fully supervised treatment, while 42.8 % received no supervision during the treatment (Ministry of Health et al. 2005). A study conducted in Chongqing in 2004 showed that only 16 % (64/401) of patients were enrolled in the DOT system and 72 % (289/401) had no supervision at all (Hu et al. 2006).

DOT management is not the only strategy in the TB prevention and control program. Many professionals agree that DOT should be performed during the intensive phase of treatment, usually for 2 or 3 months (Sun et al. 2008). If there are difficulties in conducting DOT management after this time period, then the whole course management program should be adopted for the continuation phase.

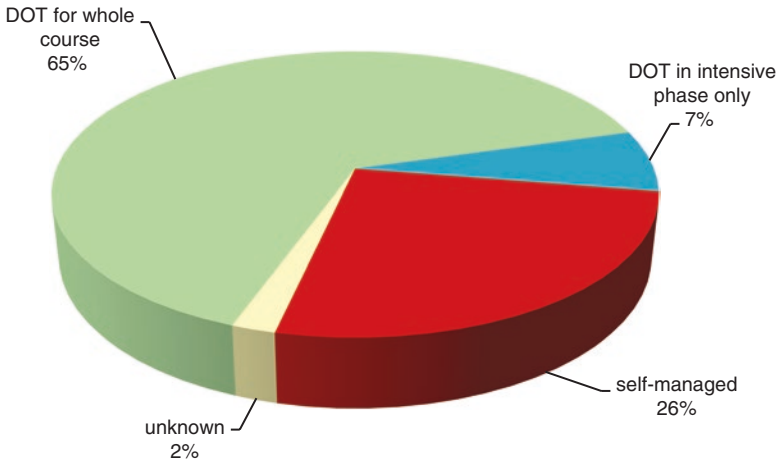

Fig. 9.2 A joint site assessment of DOT in four provinces, 2000 (Cai and Chen 2003). The WHO and the Chinese Anti-Tuberculosis Association joint site assessment, which covered four counties in each of four randomly selected provinces (Hebei, Hunan, Ningxia, and Chongqing; $n = 641$)

9.2.2 Elements That Deter the Use of DOT in China

The problems that have occurred over the years point to the difficulty of comprehensively instituting DOT in China. The elements that inhibit DOT performance in China are described below.

9.2.2.1 Regional Variation

China is a large developing country with a multitude of different economic and geographic regions, and varying transportation and healthcare infrastructures. In the expansive western region of China where the means of transportation are limited, it is difficult to implement DOT for a 6–8 month course of treatment. In a study of 401 TB smear-positive patients in four counties in Chongqing, Hu et al. found that the implementation rate of DOT varied by region (from 7.6 % in Xiushan county to 25.3 % in Rongchang county) because of economic and geographic differences (Hu et al. 2006). In other regions with well-developed healthcare systems, such as Jiangsu Province, the implementation rate of DOT was more than 90 % (Zheng et al. 2009).

9.2.2.2 Difficulties of Promoting DOT Among Patients

Attitudes towards DOT differ among patients. Most patients believe that it is not necessary to be supervised when taking medication (Hu et al. 2006; Ministry of Health, Disease Control Division et al. 2005). Some think that taking medication is

their own business, and that they can do it conscientiously on their own. Others fear that a visit from the doctor could infringe upon their privacy or interfere with their work, so they refuse supervision. However, older patients and patients who have difficulty taking medications on their own readily accept supervision (Chen et al. 2006). Management measures should be adapted according to a patient's attitude toward medical staff visits and treatment.

9.2.2.3 Total Implementation of DOT Will Increase the Burden on Both the Patient and the Healthcare System

China has the second highest number of TB patients in the world (WHO 2008). To fully implement DOT and visit each and every patient several times a week would require a very large number of treatment supervisors in a country with limited healthcare resources. This becomes particularly problematic in cases where patients live far from health centers or have work schedules that conflict with those of the medical staff. In some areas the proportion of medical staff supervisors to patients is very low (Sun et al. 2008; Hu et al. 2008). In these cases family members become the first choice to act as supervisors (Cheng and Gong 2004). In rural areas many farmers work long hours, so it is not possible for them to perform treatment supervision duties, in which case fully supervised treatment exists in name only. Lienhardt and Ogden proposed that many factors such as different attitudes towards TB, rapidly changing healthcare practices, the high cost of treatment, and social discrimination still faced by TB patients make DOT unsuitable for continuous TB prevention without external financial support (Lienhardt and Ogden 2004). Therefore, they questioned the universal application of DOT. Similar conclusions were drawn from a randomized controlled trial of TB drug resistance (Rusen et al. 2007). Khan et al. showed that the implementation of DOT is less cost-effective than self-medication management (Khan et al. 2002).

It is difficult to fully implement DOT management for the treatment of TB in many developing countries; it is complicated by the high cost of healthcare and differences in economic levels, geography, availability of transportation, and patient preferences. Though DOT is considered the best management strategy currently available and is widely recommended by the WHO (Bastian et al. 2003) its effectiveness is still controversial. It was shown in ten self-treatment management trials that DOT is not more effective than self-treatment (Volmink and Garner 2007).

Research also suggested that it is not possible to achieve the WHO's aim that 85 % of TB patients complete their treatment without other treatment support measures (Volmink et al. 2000).

A US study of 122 TB patients taking isoniazid and *para*-aminosalicylic acid (PAS) from automatically monitored medicine dispensers showed that 60.7 % of the patients finished 90 % of the full 18–24 month course of medication, and 82.3 % of the patients had taken 70 % of the full course (Moulding et al. 1970). Many studies have shown that a patient's medication compliance decreases with a rise in drug dosage (Claxton et al. 2001). In a Canadian study of 104 patients infected with

latent TB, the overall completion rate for treatment was closely related to the completion rate for the first month. Those who took medicine at the same time every day were more likely to finish the medication regimen (Menzies et al. 2005). A study of active TB patients in Haiti indicated that patients whose treatment compliance was ≥90 % in the first 11 weeks showed 3 times the compliance rate after 1 year than the patients whose treatment compliance rate was <90 % in the first 11 weeks. Moreover, the probability of treatment failure for patients whose treatment compliance was <90 % in the first 11 weeks was 6 times that of patients whose treatment compliance was ≥90 % in the first 11 weeks. These studies showed that the record of patient's medication early in treatment can help to predict the patient's compliance and the overall treatment result (Moulding and Caymittes 2002).

These studies support the idea that patients with good compliance can successfully self-medicate, and additional treatment measures should be reserved for those with poor compliance. There are about one million active TB patients diagnosed each year in China. When dealing with such a large epidemic, it would seem reasonable to target different populations and patients with different management strategies instead of employing a single strategy across the board, even one as well established as DOT.

9.3 Exploring the Proper Model for TB Patient Management in China

9.3.1 The New International Concept

New international standards no longer mandate DOT for all patients. Medical staff not only need to develop the right treatment program, but also must be able to assess the compliance of patients and deal with any irregular treatment issues (Tuberculosis Coalition for Technical Assistance 2006). The WHO's current Stop TB Strategy clearly states that DOT management should be applied differently according to the different individual conditions (WHO 2006). Patients should take medication regularly, and supervisors should provide appropriate service and support. Meanwhile, DOT could be performed not only in health institutions, but also in the workplace, community, and home. The supervisor must be someone who is willing to accept guidance from healthcare institutions and is accepted by the patient.

The WHO strongly recommends that communities play a role in TB prevention, treatment, and supervision. Local community workers have firsthand knowledge of an individual patient's compliance based on treatment records. Additional attention should be given to those with poor compliance. By targeting supervision in this way, fewer supervisors can have a greater impact on overall community compliance. It is important to develop proper models for TB patient management that make full use of the limited health resources.

9.3.2 *Exploring a New Model of Management for Chinese TB Patients*

At present, DOTS is still the standard TB control strategy used in patient management in China. However, considering the limitations of DOT, China has begun to explore new management strategies appropriate for TB patients.

9.3.2.1 Policy Adjustment

Since 2009, China's TB control program has expanded the kinds of supervisors used for DOT implementation to include family members and volunteers, as used in the Shanghai program, nationwide. In general, village doctors should supervise the patient as he or she takes the anti-TB drugs. If the patient's home is far from the village health station (more than 1.5 km), the family members or volunteers will supervise the patients taking the anti-TB drugs.

9.3.2.2 Research on New Management Strategies

It has been suggested that written reminders including dosage, method, and time should be placed somewhere that patients often look, such as at the bedside, kitchen table, or near drinking cups in order to improve compliance. In a small study in South Africa, patient compliance improved from 62.0 to 88.0–93.0 % after dosage cards were provided (Sonnenberg et al. 1998). In an Indian study, 200 patients released after 1 month of hospitalization were divided into two even groups. Patients from one group were mailed up to two reminder cards if they failed to pick up their monthly allocations of medicine; patients from the second group did not receive notices. The treatment completion rate was significantly higher for patients who had received the reminder cards (88 %) than for those who did not (73 %). About 30 % of each group defaulted; the recovery rate in the group receiving reminders was significantly higher (58.6 %) than in the control group (12.9 %). Interestingly, the recovery rate observed was still significantly higher in the reminder group for illiterate patients (Paramasivan et al. 1993).

In 2010, with funding from the Chinese Ministry of Health and the Bill & Melinda Gates Foundation, China began a TB control study on the feasibility and operability of new treatment methods for different categories of patients. The study, organized and implemented by the National Center for TB Control and Prevention of the China CDC, was conducted in 36 counties in Chongqing, Jiangsu, Heilongjiang, and Hunan provinces. Patients were assigned to one of three intervention arms for reminders to take their medication on days of drug intake. In the mobile phone arm (971 cases) patients received an SMS with the text "please take the medication on time" and were asked to reply to the SMS. Patients in the medication monitor arm (969 cases) had a medication monitor box in reminding mode, so

that it beeped to remind them to take their medication. Patients in the combined mobile phone and medication monitor arm (1013 cases) were reminded to take their medication by both methods.

E-Pill Box Technology

The e-pill box was designed by the National Center for TB Control and Prevention of the China CDC and is used for holding and dispensing pills. It automatically records the time the case is opened. A voice ("please take the medication on time") or music is used to remind the patient to take pills regularly, or to go to the local TB institution for scheduled refills. The e-pill box was provided with a 1-month supply of anti-TB drugs to patient volunteers. The patient's healthcare provider set the reminder time for taking medication according to the patient's requirements. Patients were required to go to the TB control agency every month with the box to get their follow-up medication, where the medical staff collected the records and assessed compliance. The records showed when the box was opened, though this does not guarantee the patient had taken the medication. If a patient had missed a dose three to six times per month, doctors at the village level would perform weekly home visits to reinforce the medication process. If the patient missed medication more than seven times in a month, or missed three to six times in a month for a second time, strict supervision of medication was enforced and the patient was enrolled in DOT management.

Based on each patient's compliance using the e-pill box, researchers were able to classify patients into different programs to ensure all patients completed their treatment and apply healthcare resources more efficiently. Patients with good compliance were allowed to continue to use the e-pill box, and patients with poor compliance were enrolled in DOT with counseling and supervision.

Short Message Service (SMS) Technology

With the rapid development of China's telecommunication industry, mobile phone use has become quite extensive. Strong cell phone reception coverage has reached even more remote rural areas. Cell phones are small, easy to carry, and are convenient for sending and receiving messages. This provides a new opportunity for patient management, as they are a suitable tool for patient communication. SMS was used to manage the treatment process, making it easier for medical staff to monitor the patient's medication situation at any time. Short text messages were sent to patients' cell phones to remind them to take medication. After taking medication, the patients were supposed to reply with a confirmation text message. During treatment, the system would send patients occasional updates containing health knowledge and, when appropriate, remind them to pick up monthly refills. Healthcare providers assessed each patient's compliance based on the text message record. If the record showed several missed treatments, doctors were required to take the appropriate steps to enhance treatment management.

This randomized pilot study is expected to establish a new model for treatment management that utilizes the e-pill box and SMS technology combined with incentives for medical personnel. The current pilot study has been completed, but the results have not been published as of this writing. Compared to DOT, this new model is easier to implement, is less costly, and requires less manpower. Preliminary data shows that the application of the e-pill box and SMS has been accepted by both medical personnel and patients, and suggests these methods improve patient compliance to ensure complete treatment.

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Chapter 10
Drug-Resistant TB

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10.1 The Rise of Drug-Resistant Tuberculosis

Since the initial use of streptomycin to treat tuberculosis (TB) in 1943, the incidence of TB strains resistant to therapeutic antibiotics (drug-resistant TB, DR-TB) has continued to increase. The widespread use of rifampicin in the 1970s led to the emergence of multidrug-resistant TB (MDR-TB) strains resistant to both rifampicin and isoniazid. Subsequently, second-line drugs were launched in treatment of MDR-TB. Improper use of second-line drugs accelerated the generation and spread of extensively drug-resistant TB (XDR-TB). In addition to rifampicin and isoniazid, XDR-TB is resistant to any fluoroquinolone and at least one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin). Since the first case report of XDR-TB was published in 2005, XDR-TB has been found in every area of the world.

In 2008, the World Health Organization (WHO) released data on the prevalence of DR-TB based on data from more than 25 million TB patients in 116 countries.

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The data showed that among incident TB cases, the prevalence of a single drug-resistant strain was 17.0 % (95 % CI: 13.6–20.4) and the prevalence of MDR-TB was 2.9 % (95 % CI: 2.2–3.6). Among previously treated patients, the prevalence of one drug-resistant strain was 35.0 %, and the prevalence of MDR-TB was 15.3 % (95 % CI: 9.6–21.1). Among all TB patients, the prevalence of one drug-resistant strain was 20.0 % (95 % CI: 16.1–23.9), and the prevalence of MDR-TB was 5.3 % (95 % CI: 3.9–6.6) (WHO 2008a).

In 2007, there were 9.27 million TB patients worldwide, 500,000 of whom were infected with MDR-TB. The vast majority of the MDR-TB patients (85 %) were distributed across 27 countries, 15 of which were in Europe. The top five countries in terms of total number of MDR-TB cases were: India (131,000), China (112,000), Russia (43,000), South Africa (16,000), and Bangladesh (15,000). By the end of 2008, a total of 55 countries had reported at least one MDR-TB case (WHO 2009b).

Although some progress has been made in reducing the global TB burden, the increasing incidence of DR-TB cannot be ignored. Before the 1990s, the prevalence of drug-resistant TB was less than 5 % in incident TB cases. Since then, the incidence of DR-TB has increased on a yearly basis (Ye 2008). In 2008, it was estimated that 44 million people were suffering from MDR-TB worldwide. The WHO's 2010 report on M/XDR-TB noted a significant increase in the proportion of drug-resistant cases among newly found TB patients. In some parts of the world, one in every four TB patients will develop DR-TB that cannot be cured by standard therapeutic methods. Asia bears the brunt of the global TB burden. Nearly 50 % of the world's MDR-TB cases occur in China and India. In Africa, the number of incident TB cases is estimated to be 6.9 million, the vast majority of which were misdiagnosed (WHO 2010a).

10.1.1 The Chinese DR-TB Epidemic

The 2007–2008 Chinese national survey on DR-TB found that among pulmonary-TB cases, the prevalence of MDR-TB was 8.3 % and the prevalence of XDR-TB was 0.68 %. Among smear-positive TB cases being treated for the first time, the prevalence of MDR-TB was 5.71 % and that of XDR-TB was 0.47 %. Among smear-positive TB cases that had been treated more than once, the prevalence of MDR-TB was 25.64 % and that of XDR-TB was 2.06 %. China has 120,000 new cases of MDR-TB and 10,000 new cases of XDR-TB per year. This is the second highest case burden in the world and accounts for 24.0 % of total cases in MDR-TB worldwide (Tang 2009).

10.1.2 Development of Drug Resistance

Primary drug resistance is defined as DR-TB that has developed in patients with no history of treatment for TB (Tang 2009; Tu 2007; Andini and Nash 2006). It occurs when a person is either infected with a drug-resistant strain of *Mycobacterium*

tuberculosis or with a "sensitive" strain that mutates into a drug-resistant strain after infection. Natural resistance refers to the spontaneous occurrence of drug-resistant bacteria during the proliferation of a wild strain of *M. tuberculosis*. Canetti and Grosset (1961) discovered isoniazid-resistant bacteria during growth of wild *M. tuberculosis* in Löwenstein–Jensen (LJ) medium. David (1980) confirmed this by developing several drug-resistant strains under similar conditions. The frequency of resistant mutants has been determined for each drug: isoniazid (H) 3.5×10^{-6}, streptomycin (S) 3.8×10^{-6}, rifampin (R) 3.1×10^{-8}, ethambutol (E) 0.5×10^{-4}, pyrazinamide (Z) $10^{-2\sim-4}$, fluoroquinolones $10^{-5\sim-6}$.

Acquired drug resistance develops as a result of ineffective treatment and/or noncompliance, which leads to an initial sharp decline in nonresistant bacteria and a subsequent overgrowth of drug-resistant bacteria. The probability of TB developing resistance is a function of the quantity of bacteria and the frequency of natural mutation. It can be calculated using the formula $P = 1 - (1 - r)n$, where P is the probability of developing acquired drug resistance, r is the probability of developing natural drug resistance, and n is the quantity of bacteria in the infected tissues (Tang 2009; Tu 2007, Andini and Nash 2006).

Employing combination therapy treatment with several effective drugs simultaneously can significantly reduce the chance of a patient developing resistant mutants. However, in order to prevent or significantly reduce the chances of generating drug resistance, it is crucial to adjust the dosage of the drugs based on the amount of bacteria in the tissues. In brief, acquired drug resistance is directly related to improper treatment and/or noncompliance.

10.1.2.1 Treatment Failures Leading to DR-TB

Multidrug therapy (MDT) is one of the guiding principles for treating TB. However, many clinicians have violated this principle by prescribing an inadequate quantity and/or variety of drugs. This is particularly problematic in areas where severe cases of TB predominate, where the prevalence of primary drug resistance is high, and where TB surveillance is poor. Providing inadequate MDT increases the probability of developing drug-resistant or multiple drug-resistant TB (Tang 2009; Tu 2007; World Health Organization 2008a, b, c; Morris et al. 2005; Chang et al. 2004; Mak et al. 2008).

Inconsistent treatment is the primary reason for the rise of DR-TB. Many patients do not take their medication on a regular basis or do not complete the full course of treatment in the mistaken belief that initial improvement in symptoms is a sign that they have been cured. Interruption of treatment can also be caused by adverse drug reactions, economic difficulties, or poor quality patient supervision and/or support provided by healthcare providers. Due to the variety of anti-TB drug pharmacodynamics, pharmacokinetics including plasma peak and the minimal inhibitory concentration (MIC) ratio, and different pathological organization peaks, regular treatment is an important guarantee for effective treatment (Tang 2009; Tu 2007; World Health Organization 2008a, b, c; Morris et al. 2005; Chang et al. 2004; Mak et al. 2008).

Insufficient quantity and an incomplete range of drugs available are the most common problems with drug supply. Low-quality and unguaranteed drug supplies have become further factors in producing drug-resistant TB. If there are similar supply problems with second-line drugs, resistance to them will develop and the difficulties of treating TB will be compounded. These problems are particularly prominent in developing countries (Tang 2009; Tu 2007; World Health Organization 2008a, b, c; Morris et al. 2005; Chang et al. 2004; Mak et al. 2008).

Other patient factors may play a role. TB patients with comorbidities, including liver and kidney disease, gastrointestinal disease, cardiovascular dysfunction, and neuropsychiatric disorders, often cannot tolerate standard anti-TB treatment. Adjusted (reduced) chemotherapy usually does not achieve the desired therapeutic effect, making patients more susceptible to developing drug-resistant infections. Some patients with comorbidities have poor oral drug absorption, and some have adopted unhealthy lifestyles involving drug and alcohol abuse. Both can reduce the effectiveness of treatment and lead to the development of drug resistance (Tang 2009; Tu 2007).

10.1.3 Transmission of DR-TB

As with drug-sensitive TB, DR-TB is transmitted through the inhalation of infectious aerosol droplets expelled from the lungs of an infected person. The primary source of infection is patients who are sputum smear- or culture-positive. The sputum of patients infected with DR-TB turns negative more slowly after treatment than that of patients infected with drug-sensitive TB. In fact, some DR-TB patients may end up becoming chronic carriers of TB.

When patients with active TB cough, sneeze, or speak loudly, droplet nuclei with mycobacteria at their core form, and are suspended in the air. Droplets can remain airborne on their own or may contaminate dust particles. Inhaling a single nucleus with as few as ten mycobacteria can lead to infection. When droplet nuclei containing DR-TB enter a host, any resulting TB infection will be drug resistant.

Factors such as diabetes, silicosis, cancer, organ transplantation, long-term use of immunosuppressive drugs or corticosteroids, HIV/AIDS, poverty, poor living conditions, and malnutrition contribute to the high incidence of TB in less developed countries. Close contact with DR-TB patients increases the risk of contracting DR-TB. Children, the elderly, and immune-compromised individuals are at particularly high risk. Research has shown that people who come into close contact with MDR-TB patients usually contract DR-TB if and when they develop active TB (WHO 2008c). In addition, medical staff, especially those working in TB isolation rooms, TB treatment rooms (where coughing is encouraged for the purpose of sputum induction), or in ambulances which transport TB patients, will inevitably inhale contaminated droplet nuclei and are thus at high risk for infection.

10.1.3.1 Transmission Risk Factors

Sputum smear-positive TB patients are more likely to infect others who come in contact with them than smear-negative patients. Untreated sputum-positive patients have a higher possibility of transmitting TB to others as compared to sputum-positive patients under treatment. Because DR-TB patients have a longer period of time until sputum conversion, thus remaining sputum-positive longer with continued respiratory symptoms such as cough and sputum production, they are more likely to infect others.

Environmental factors also play a role. Because TB is a contagious respiratory disease, ventilation of patients' living space is crucial. The patient may spend time outdoors, weather permitting, but when it is too cold or hot outside, patients usually stay indoors with the windows tightly closed. Being in a closed environment, whether in a residence with family members or in a hospital with healthcare workers, can lead to the spread of DR-TB, especially among close contacts. Close contacts spend several hours a day in the same household or in the same room with a DR-TB patient and may be relatives or health workers (WHO 2008c). Immune-compromised people, such as children and the elderly, are very susceptible to infection with DR-TB and may further spread the disease. If not effectively protected, health workers also have a high risk of infection.

Additionally, patients living in poverty may not have the financial resources to receive or complete treatment, making them a continual source of infection due to ineffective control of their illness. These patients also have a higher chance of developing DR-TB, MDR-TB, or XDR-TB, and end up becoming a very dangerous source of infection.

Suffering from DR-TB is a tremendous blow to both patients and their families, and thus requires care and support from doctors, nurses, community workers, and family members. Lacking knowledge of this disease may lead to discrimination against patients, interfere with treatment compliance, or cause patients to abandon treatment and participate in activities and behaviors that may promote the spread of this disease.

In some low-resource areas, hospitals have insufficient ward space and multiple patients often share the same room. In non-TB-designated hospitals, doctors may fail to diagnose TB in time, resulting in TB patients sharing space with patients infected with noncommunicable diseases, which leads to the spread of TB within the hospital. Doctors lacking the experience or facilities to conduct TB drug sensitivity testing may fail to initiate an appropriate anti-TB treatment, resulting in ineffective and delayed treatment that increases the chance of transmission of DR-TB to others.

10.1.3.2 Host Factors

Certain host genetic factors may play an important role in the occurrence, development, and relapse of DR-TB. For example, HLA-DRB1*14 is a risk factor for independent MDR-TB in the Indian population (Rajalingam et al. 1996). Among the

Japanese population, SLC11A1, D543N, and 3′UTR gene polymorphism are significantly associated with the occurrence of MDR-TB (Takahashi et al. 2008).

Recent results from global TB drug resistance monitoring show that there is a certain correlation between HIV and MDR-TB in some parts of the world. Although relevant factors behind this have not been clearly defined, HIV infection is a significant risk factor for the outbreak of TB and DR-TB, including XDR-TB (WHO 2008a; Gandhi et al. 2006). After HIV infection, the immune function of anti-TB cells is suppressed, rendering the immune system unable to prevent the growth and dissemination of *M. tuberculosis*. While studies have shown that approximately 10 % of people infected with TB will develop an active infection, nearly half of all HIV patients infected with TB will develop active TB. Meanwhile, TB infection plays a key role in the invasion of CD4 cells, proviral transcription, latency and dissemination of HIV. Therefore, the global HIV/AIDS epidemic is an important factor in the transmission of TB and DR-TB.

10.2 DR-TB Control Strategy

In order to curb DR-TB, the WHO has extended its Directly Observed Therapy, Short-course (DOTs) program to include control of MDR-TB. This is known as "The Stop TB Strategy." This strategy contains the following elements:

1. Pursue high-quality DOTS expansion and enhancement.
2. Secure political commitment with adequate and sustained financing.
3. Ensure early case detection and diagnosis through quality-assured bacteriology.
4. Provide standardized treatment with supervision and patient support.
5. Ensure effective drug supply and drug management.
6. Monitor and evaluate performance and impact.
7. Address TB-HIV, MDR-TB, and the needs of poor and vulnerable populations; scale-up collaborative TB/HIV activities; scale-up prevention and management of MDR-TB; and address the needs of TB contacts, and of poor and vulnerable populations.
8. Contribute to health system strengthening based on primary health care; help improve health policies, human resource development, financing, supplies, service delivery, and information; strengthen infection control in health services, other congregate settings and households; upgrade laboratory networks, and implement the Practical Approach to Lung Health (PAL); adapt successful approaches from other fields and sectors; and foster action on the social determinants of health.
9. Engage all care providers; involve all public, voluntary, corporate, and private providers through Public-Private Mix (PPM) approaches; and promote use of the International Standards for Tuberculosis Care (ISTC).
10. Empower TB patients and communities through partnership; pursue advocacy, communication and social mobilization; foster community participation in TB

care, prevention and health promotion; and promote use of the Patients' Charter for Tuberculosis Care.
11. Enable and promote research; conduct program-based operational research; and advocate for and participate in research to develop new diagnostics, drugs, and vaccines (WHO 2008c).

The WHO's "Stop TB Strategy" also contains the following elements for early detection of DR-TB:

1. Conduct drug resistance testing on people at higher risk of developing DR-TB.
2. Conduct multidrug-resistant screening for patients at higher risk of developing MDR-TB.
3. Conduct preliminary screening for MDR-TB among HIV-infected individuals who routinely receive drug susceptibility testing.
4. Conduct susceptibility testing for isoniazid, rifampicin, second-line injections, and any fluoroquinolone among patients at high risk of developing XDR-TB.

The "Stop TB Strategy" also recommends the implementation of directly observed therapy (DOT) for all TB patients if allowed under treatment protocol. Ensuring medication adherence helps prevent drug-resistance.

10.3 DR-TB Mortality

The current cure rate for TB patients being treated for the first time has reached 90 %. However, the mortality rate for patients with DR-TB is significantly higher than that of patients with drug-sensitive TB. In 2008, there were an estimated 9.4 million newly diagnosed TB cases and 1.8 million TB deaths globally. Among these new cases, more than 440,000 were MDR-TB, of which 150,000 resulted in death. There are no official estimates for the number of XDR-TB cases, but there are approximately 25,000 deaths from XDR-TB each year (WHO 2010a). The KwaZulu-Natal cohort study in South Africa showed that among HIV/XDR-TB co-infected individuals, the mortality rate was as high as 98 % with a median time to death of only 16 days after specimen collection (Gandhi et al. 2006).

10.3.1 DR-TB Will Cost More Social Resources

The standard 6-month treatment regimen [2S(E)HEZ/4HR] does not work for DR-TB. It may require more than 2 years of treatment with drugs that are more toxic and cost 50–200 times more than those used in standard TB treatment. A standard 6-month drug regimen for sensitive TB cost about $20, while treatment for MDR-TB can cost up to $5000. Treatment of XDR-TB is even more expensive.

In 2009, the total cost for the 22 high-TB burden countries to fully implement their national plans for TB control was $2.9 billion, 69 % of which was for DOTS ($2.0 billion). Much of the remainder was devoted to MDR-TB control (14 %, or $400 million). The funds actually available to these countries in 2009 amounted to approximately $2.2 billion, a shortage of nearly $800 million (WHO 2009b).

In addition, patients infected with DR-TB are usually unable to work and cannot participate in a normal social life. This creates tremendous physical, emotional, and financial hardship for patients and their families. As a result, health workers are required to spend more time and energy managing the treatment of these patients.

10.3.2 Measures to Avoid the Occurrence of DR-TB

1. As inappropriate treatment of newly diagnosed TB patients or first relapsed TB patients is a major contributing factor in the rise of DR-TB, it is critical to effectively treat these patients. This may be difficult due to poor resources (an inability to perform drug susceptibility tests or inadequate supply of medicine) or because of poor patient compliance (Xiao 2010a, b).
2. Implement the DOTS strategy for the management of drug-resistance to improve the cure rate for DR-TB.
3. Infection control of DR-TB. Infection control measures include: management control, environmental control, personal respiratory protection (special masks), etc. (see Sect. 5.4).

10.3.3 DR-TB: A Global Public Health Threat

Since the 1950s, the continual discovery of effective anti-TB drugs has kept the transmission of TB under control in many countries, and given the appearance that the disease was under control and that it would be eliminated some day. As a result, many countries have reduced their financial expenditures on TB control. This reduction in spending to control TB, combined with population growth, increased population mobility, and the spread of infectious HIV, has contributed to the resurgence of the TB epidemic. In 1993, after the discovery of MDR-TB and its spread, the World Health Organization declared TB to be a global health imperative. In 2005, physicians in a rural hospital in the KwaZulu-Natal Province in South Africa observed an extremely high mortality rate among HIV positive patients co-infected with TB. They determined that these patients were all infected with XDR-TB. In March 2006, the WHO and the United States Center for Disease Control and Prevention (CDC) confirmed the presence of XDR-TB in the United States (CDC 2007). By the end of 2010, at least one case of XDR-TB was reported in 69 countries and territories (WHO 2011b). WHO Director-General Dr. Margaret Chan has stressed that

"tuberculosis has again placed the world in a precarious situation, which is already alarming, and it is poised to grow much worse, very quickly" (WHO 2009d).

If MDR-TB is not forcefully addressed, it stands to replace the drug-susceptible strains that are currently responsible for 95 % of the world's TB cases. Left unchecked, XDR-TB could take us back to an era that predates the development of antibiotic treatment of TB.

10.3.3.1 Hazards DR-TB Poses to Human Health

More than two billion people—one-third of the world's total population—are infected with *M. tuberculosis*, the microbe that causes TB. Of that number, about 50 million are infected with TB that is resistant to one or more drugs. One in ten of those infected with DR-TB will become sick with active TB in his or her lifetime. People living with HIV develop active TB at a much higher rate. Left untreated, each person with active TB disease will infect on average between 10 and 15 people every year. People with DR-TB are even more infectious (see Sect. 4).

The proportion of primary M/XDR-TB cases has increased annually since 2002, indicating that these cases were multidrug resistant at the time of infection, and not as a direct result of substandard treatment. This is truly alarming and warns us that resistant strains are now circulating among the general population, spreading widely and silently, in the growing pool of latent infection.

10.4 Identification and Diagnosis of DR-TB

Patients should be considered to have a high risk of DR-TB if there is suitable supporting evidence. The possibility of drug resistance needs to be taken into account in cases of treatment failure (defined as a case that is sputum smear-positive after 4 months of treatment under standard guidelines, or a sputum culture-negative case that later becomes positive). If there is no improvement in clinical symptoms and/or if the patient becomes sputum smear-positive after the first time of treatment, DR-TB may be suspected. Recurrence may also suggest DR-TB. Recurrence is defined as a case that had got sputum smear negative or culture conversion but subsequently becomes sputum-positive after anti-TB treatment, and the patient presents clinical or radiological evidence to suggest deterioration due to TB. Other factors to be considered are whether the patient has a history of close contact with DR-TB patients or is from DR-TB endemic areas (residential areas with a high prevalence of DR-TB or institutions that have had outbreaks or epidemics of DR-TB). Other factors that can put patients at high risk of DR-TB infection include a history of using anti-TB drugs of poor or unknown quality, infection with comorbid conditions associated with malabsorption or rapid-transit diarrhea, and residence in areas with poorly operated and implemented treatment centers (especially those with recent and/or frequent drug stockouts).

10.4.1 DR-TB Patient Diagnostic Strategy

1. Perform susceptibility testing for all patients who are at increased risk of developing DR-TB.
2. Perform susceptibility screening for all patients who have a high risk of developing MDR-TB.
3. Perform regular drug susceptibility testing for individuals with HIV. If possible, perform rapid susceptibility testing as an initial screening.
4. Drug susceptibility testing for isoniazid, rifampicin, second-line drugs including injectable agents and fluoroquinolones should be performed for patients with risk factors for XDR-TB.

10.4.1.1 Evaluations of Drug-Resistant TB Diagnostic Techniques and Methods

Diagnosis of DR-TB includes culture and strain identification as well as drug susceptibility testing (DST). The result of DST is the sole criterion for diagnosis of DR-TB and is critical information in the development of a DR-TB treatment plan (WHO Guidelines 2008c; WHO 2009c, hereinafter WHO Guidelines 2009; Richter et al. 2009; Tang 2009; Van Deun et al. 2010). Techniques for diagnosing DR-TB include phenotypic and genotypic tests. Traditional phenotypic culture-based DST involves the inoculation of a clinical specimen onto/into media containing specific concentrations of anti-TB drugs, and then observing whether the growth of *M. tuberculosis* is inhibited. The phenotypic DST method can be directly or indirectly performed on solid medium. The direct method involves inoculating what is derived from a pure culture onto/into a medium that either contains or does not contain anti-TB drugs. In the indirect method, inoculum is derived from a decontaminated clinical specimen and then tested by corresponding methods including the absolute concentration method, resistance ratio method, and ratio method. The indirect method is the most commonly used and widely recognized, and thus remains the gold standard for phenotypic-based DST (WHO 2008c; WHO 2009c; Richter et al. 2009; Tang 2009; Van Deun et al. 2010). For first-line anti-TB drugs, all three methods of DST can be performed with a high degree of reliability and repeatability. For second-line drugs, the indirect proportion method is more reliable. The reliability of the absolute concentration method and the resistance ratio method for second-line drugs is undetermined (Tang 2009; Van Deun et al. 2010; WHO 2008a). Rapid liquid culture and drug susceptibility testing methods include: BACTEC™, Etest®, and MB-Bact among others (Martin et al. 2009; Rishi et al. 2007; Verma et al. 2010). The BACTEC method is reliable and repeatable when testing first-line anti-TB drugs and thus can replace conventional phenotypic assays; however, its effectiveness testing second-line drugs is uncertain. The reliability and effectiveness of Etest and MB-Bact remain to be studied.

Genotypic methods test for the presence of gene mutations responsible for drug resistance. The most studied genotypic method is rapid rifampicin resistance detection. It is now commonly agreed that in most cases, especially in areas that use fixed-dose combination first-line anti-TB drugs, resistance to rifampicin almost always accompanies resistance to isoniazid. Thus, if an infection is determined to be rifampicin resistant, it very likely means the infection is MDR-TB. The most commonly used method for testing rifampicin resistance is the Genotype Mycobacterium Tuberculosis Drug-Resistance (MTBDR) test. This method can diagnose rifampicin-resistance with high accuracy. It also has high specificity for the diagnosis of isoniazid resistance but low sensitivity (Van Deun et al. 2010; Ling et al. 2008). Molecular line probe assay, or GenoType MTBDR (Hain Lifescience, Nehren, Germany), has been recognized and recommended by the WHO. The advantage of this method is its simplicity. It only takes 24–48 h to diagnose MDR-TB, and it can be used directly on smear-positive sputum samples. Recently, a new molecular line probe assay, the GenoType MTBDRsl test, designed for the rapid detection of resistance to ethambutol, fluoroquinolones, and other second-line injectable drugs, has been used to diagnose XDR-TB (Hillemann et al. 2009; Brossier et al. 2010; Palomino 2009; Langei and Mori 2010). Locked nucleic acid probe real-time PCR (LNA-PCR) can detect FQ-associated mutations in gyrase A of *M. tuberculosis* (Van Doorn et al. 2008). Gene chip technology is high in sensitivity but low in specificity, which limits its use in clinical diagnosis. Additional comparison studies are needed to compare newer methods for rapid diagnosis of DR-TB with traditional phenotypic methods (Van Deun et al. 2010; Ejigu et al. 2008; WHO 2011c).

10.4.1.2 Sequence of Susceptibility Testing

An accurate clinical diagnosis of drug-resistant TB is an essential element in the control of DR-TB. A comprehensive laboratory quality assurance program must be established to ensure the reliability and repeatability of test results. Proper use of testing techniques and methods are also important. The first step should be to perform traditional table-based detection methods as suggested by the WHO. The choice of methods should be based on the setting. The absolute concentration method, ratio method, and resistance ratio method can be applied in low resource settings, and the BACTEC method can be used in settings with better economic conditions. Drug susceptibility testing should be performed in sequence:

1. Test for susceptibility to isoniazid and rifampicin.
2. Test for susceptibility to ethambutol, streptomycin, and pyrazinamide.
3. If possible, test for amikacin, kanamycin, capreomycin, and, ideally, fluoroquinolones.
4. It is not recommended to carry out subsequent testing for group 4 and 5 drugs. The susceptibility testing of these drugs is very complicated, and there are significant methodological differences in carrying out these tests. The critical concentration level used to define drug resistance for these drugs is very close to the

minimum inhibitory concentration (MIC) level required for their antibacterial activity. This increases the difficulty in distinguishing between drug resistance and drug sensitivity. Moreover, the reliability, credibility, and repeatability of resistance testing for these drugs are uncertain, as is the association between test results and clinical therapeutic effects. Therefore, the DST results for these drugs should be used for reference only (WHO 2008c; Tang 2009; Van Deun et al. 2010; WHO 2011c).

10.5 Treatment of Patients with DR-TB

There are three kinds of treatment strategies for DR-TB: standardized, empirical, and individualized treatment (Xiao 2010a; Tang 2009; WHO 2008c). Standardized treatment uses drug resistance testing data from representative patient populations to support regimen design in the absence of individual DST data. All patients in a defined group or category receive the same regimen. An empirical treatment regimen is individually designed based on the patient's previous history of anti-TB treatment, with consideration of DRS data from the representative patient population. An individual treatment regimen is designed based on the patient's previous history of anti-TB treatment and individual DST results. There are two ways to combine these strategies: the standard treatment followed by individualized treatment; and the empirical treatment followed by individualized treatment. Standard treatment and empirical treatment allow adjustment to the regimen when DST results on the individual patient become available. The choice of treatment strategy should be based on the actual task accepted, the objectives to be achieved, and/or the specific circumstances of the region that the patient comes from. For example, the task might be to treat the patient using one standard regimen, and the objective might be to investigate the outcome of the standard regimen.

10.5.1 Chemotherapy

To facilitate the treatment of DR-TB, anti-TB drugs have been divided into five groups by the WHO: Group 1, first-line oral anti-TB agents; Group 2, injectable anti-TB agents; Group 3, fluoroquinolones; Group 4, oral, bacteriostatic second-line agents; Group 5, agents with uncertain efficacy (Xiao 2010b; Tang 2009; WHO 2008c).

The following are the basic principles for designing the treatment regimen for DR-TB:

1. At least four effective drugs should be selected, and it is often necessary to use five or more drugs, to cover all possible resistance patterns for patients with XDR-TB. In most cases, an injectable agent (Group 2) and a fluoroquinolone (Group 3) make the core of the regimen accompanied by two or three second-

line drugs and a first-line oral drug (Group 1) to which the infection is still sensitive.
2. If DST results are not readily available, an empirical regimen based on the patient's treatment history and contact history is recommended. Adjustment of the regimen may be made after the results are available.
3. One sensitive Group 2 injection shall be included in the treatment and continue to be used for at least 3 months.
4. One Group 5 drug may be considered if there are not four drugs that are likely to be effective from Groups 1–4.
5. Single- and multidrug resistance treatment usually lasts 9–18 months, and XDR-TB treatment should last 24 months or more.
6. A DR-TB treatment program comprises two phases: Phase 1 is the injection period and Phase 2 is the non-injection period. For DR-TB, the phases last 3 and 9 months, respectively; for MDR-TB, the phases last 6 and 18 months, respectively; and for XDR-TB, the phases last 12 and 18 months, respectively.
7. Daily medication is used for the full course of treatment.
8. The full treatment shall be completed under directly observed therapy (DOT).

10.5.2 The Prognosis of Patients with DR-TB

Overall, the prognosis for patients with DR-TB is worse than for patients with drug-sensitive TB. The prognosis for patients with DR-TB is dependent on the type of DR-TB the patient is infected with. The cure rate for single or multiple DR-TB is still above 85 % after 9–12 months of anti-TB treatment. MDR patients, usually resistant to two of the most effective anti-TB drugs, have a poor prognosis. Treatment for MDR-TB with second-line drugs may last for 24 months or more. Theoretically, the cure rate for MDR-TB can reach 70 % or more, but the cost of treatment for MDR-TB is 100–300 times higher than for drug-sensitive TB. Due to the high cost, adverse drug reactions, and other factors, the actual cure rate is only 50 % and the adult mortality rate for MDR-TB is 23–37 %. XDR-TB has an even worse prognosis. The cure rate is lower than 30 %, and the fatality rate is 64 % higher than that of MDR (WHO 2008a).

Inappropriate treatment, adverse drug reactions, poor drug quality or disrupted drug supply, poor patient compliance, and financial difficulties can all have a negative impact on the prognosis of patients with DR-TB.

10.5.3 Patient Care and Support

DR-TB patients usually have poor adherence to treatment, mainly because of the length of the treatment course and the number of drug types. The key elements of ensuring patient compliance are: strict implementation of DOT, aggressive

treatment, close monitoring of adverse drug reactions, education of patients and their family members on the importance of adherence to treatment, and emotional and psychological support from family and society (WHO and Stop TB Partnership 2006). DR-TB can present a traumatic experience for patients and their families. Patients may face discrimination from colleagues, family members, or neighbors. They may become depressed and anxious due to adverse drug reactions and thus abandon the treatment. The community should pay close attention to the patient's social and psychological needs and understand the patient's state of mind, and must be educated about the disease in order to provide psychological counseling at multiple levels to alleviate the patient's concerns. Only in this way will the successful completion of treatment be ensured. Medical workers, including doctors, nurses, and community healthcare workers, should always offer patients and their families educational support about DR-TB. They should be informed about how to deal with adverse drug reactions and the importance of ensuring treatment compliance. Health education should start from the beginning of treatment and last throughout the course of treatment, with easily understandable content that is in line with patients' education levels. Care and encouragement from the medical staff can improve the patients' confidence and improve the chances of curing the disease.

10.5.4 Infection Control in Patients

The WHO states that three areas—leadership, technology, and finance—must go hand in hand to effectively control infectious disease. Methods for the control of TB infection consist of:

1. Management control: establishing an office of infection control; coordinating operations across different departments; providing good ventilation in TB wards; providing necessary places for quarantine of TB patients; monitoring the implementation of infection control; timely detection and referral of patients with suspicious symptoms; providing pamphlets on the proper way of spitting and coughing; and regular training of health workers.
2. Environmental control: maintaining good ventilation by simply opening doors and windows or through mechanical ventilation; installing ultraviolet light in contaminated sites, inside ventilation pipes, mounted on the ceilings or walls, or on mobile devices, ensuring that direct contact between the light and skin or eyes is prevented; and wearing personal protection such as masks or respirators designed to ensure a close fit with the face to minimize leaks and prevent inhalation of harmful small airborne particles. Ordinary masks are limited in their ability to filter infectious particles and are loose fitting and thus cannot provide adequate protection to the wearer. However, they do offer some protection, though limited, by reducing the number of droplet nuclei that can be inhaled by susceptible MDR-TB patients. This means that loose-fitting masks could be

worn by patients. A respirator is a close fitting surgical mask with special filter media used to cover the nose and mouth. The N95 is an effective and simple type of personal respirator that may be reused given its relatively high price.

10.5.5 Quality and Supply of Drugs

The provisions of the Drug Management Manual published by the Chinese Food and Drug Administration Bureau should be strictly followed to ensure an undisrupted supply of anti-TB drugs. Institutions should assign personnel dedicated to the implementation and management of the drug policy. Technical training should be offered to the drug management staff on a regular basis to strengthen their expertise and professional knowledge. Countries must develop rules for the production and use of anti-TB drugs, with an emphasis on the monitoring and regulation of second-line drugs and the standardization of procedures for handling adverse drug reactions.

10.6 Future Trend of Drug-Resistant TB

Multidrug-resistant tuberculosis (MDR-TB) refers to the TB strain resistant to at least isoniazid and rifampicin, two major first-line drugs. According to WHO estimates, 440,000 (CI 95 %: 390,000–510,000) new MDR-TB cases emerged globally in 2008. 3.6 % of new TB cases were MDR-TB (CI 95 %: 3.0–4.4) (WHO 2010a). The emergence of resistance to anti-TB drugs, and particularly the emergence TB (MDR-TB), has become not only a challenge for TB control, but also a major public health problem.

There are different views on the future trends of drug-resistant TB. Optimistically, the epidemiology of MDR-TB is in a low-prevalence stage. According to the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance, the MDR rates in new pulmonary TB cases in the Baltic countries of Estonia, Latvia, and Lithuania are 13.3 %, 10.8 %, and 9.8 %, respectively, which are higher than the global average level. In some areas of Russia and China, the MDR-TB rate in new PTB cases is very similar: the MDR-TB rate is 15.0 % in Tomsk Oblast in Russia and 7.3 % in Inner Mongolia in China (Wright et al. 2009). But the prevalence of MDR-TB of other countries or districts are below 5 % overall, indicating that the epidemiology of MDR-TB is in a localized stage (Dye and Espinal 2001). According to mathematical models, the proportion of isoniazid-resistance and MDR are close to “saturation” and not likely to exceed 5 % (Dye and Espinal 2001). Dye (2009) has argued that by means of strong measures of control and prevention, the proportion of MDR-TB in all TB cases could be reversed. Through strong political commitment and enough funding, the United States and Hong Kong

Special Administrative Region (SAR) have both reversed the trend of both TB and MDR-TB. Furthermore, according to the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance, the prevalence and case load of MDR-TB cases was reduced much faster than the prevalence and case load of all forms of TB (Wright et al. 2009). Recently published molecular biology research shows that the fitness of the strain that is resistant to isoniazid—the strain's ability for dissemination, proliferation, and survival—will decrease (Van Soolingen et al. 1999; Dye et al. 2002).

On the other hand, Sally Blower and Tom Chou formulated a mathematical model to simulate competition of different strains and evolution trends of predominant strains by setting up different schemes of case detection, treatment rate, amplification probability of pre-MDR to MDR, the fitness of MDR strains or relative transmissibility and virulence, and the cure rate of pansensitive TB. The model has considered three different mechanisms of generation of MDR-TB: (1) transmission of drug-resistant strains to uninfected individuals (transmitted resistance); (2) conversion of wild-type pansensitive cases to drug-resistant cases during treatment (acquired resistance); and (3) the progressive acquisition, by drug-resistant strains, of resistance to more drugs during repeated treatment episodes (amplified resistance). The research found a positive correlation between the epidemic of MDR-TB and the treatment availability and cure rate of pansensitive TB. If case detection and treatment rates were high (40–70 %), the area had a greater chance to become a hot zone, even with a relatively low amplification probability and transmissibility or fitness. In other words, there is no direct correlation between amplification probability and transmissibility or between fitness and the probability of becoming a hot zone (Blower and Chou 2004).

However, no matter which model of MDR-TB is used, carrying out multidrug-resistant TB standard chemotherapy, and at the same time preventing its further spread, has become the accepted focus of the field of TB control today.

10.7 The Urgent Need for New Treatment Medicines

TB is an ancient disease. In the 1940s, with the discovery of streptomycin, the first antibiotic treatment for TB, there came a series anti-TB drugs including p-aminosalicylic acid, isoniazid, pyrazinamide, ethambutol, and rifampin, which began the chemotherapy era of TB treatment. By the 1990s, the emergence of DR-TB and MDR-TB signaled the "resurgence" of TB worldwide. TB drug resistance became increasingly common and now MDR-TB is a major disease that poses a serious threat to worldwide public health. The development of anti-TB drugs is progressing very slowly and cannot meet the clinical needs of the majority of TB patients. Therefore, there is an urgent need to develop new anti-TB drugs for emerging DR-TB.

10.7.1 Sharp Increase in DR-TB

There was a global resurgence of TB beginning in the late 1980s. According to a report by the WHO, in 2008 one-third of the world population was infected with *M. tuberculosis* with 800 million new cases and 2 million deaths each year (WHO 2008a). In 2009, the WHO estimated that 3.3 % of new TB cases were MDR-TB. In 2008, approximately 440,000 MDR-TB cases emerged, resulting in 150,000 deaths (WHO 2010a). By the end of 2010, at least one case of XDR-TB was reported in 69 countries and territories, and it is estimated that every year there are 25,000 new cases of XDR-TB globally (WHO 2011b).

TB is treated with a relatively long course of combination chemotherapy. Treatment of first time patients with the first-line anti-TB drugs (including isoniazid, rifampicin, pyrazinamide, streptomycin, and ethambutol) usually takes 6–9 months. If patients are infected with DR-TB and develop tolerance to first-line anti-TB drugs, second-line anti-TB drugs such as amikacin, propylthiouracil isonicotinoyl amine, fluoroquinolones, and *p*-aminosalicylic acid are considered. These second-line drugs can cause serious adverse reactions in patients, cost much more than first-line drugs and have lower efficacy. Treatment with second-line drugs usually lasts 12–18 months. Prolonged treatment can lead to drug toxicity, reduced patient compliance, and the development of DR or MDR strains of TB (WHO 2011b). Treatment of MDR-TB requires the use of more than five different effective anti-TB drugs for as long as 24 months. In countries with the most comprehensive TB control programs, the best case cure rate for MDR-TB is only 70–80 %, and the cure rate among less developed countries is even lower. The emergence of XDR-TB has brought an unprecedented global catastrophe. Because it does not respond to any of the current anti-TB drugs, XDR-TB is an incurable disease with a high mortality rate (WHO 2011c). The existence of latent XDR-TB in patients with active TB further adds to the difficulty of treatment.

Given such severe circumstances, it is a global imperative to speed up anti-TB drug research and development in the hopes of reducing the current 6–9 months of treatment to 1–2 months (WHO 2010a). Moreover, the new treatment must also be affordable and manageable to patients.

10.7.2 HIV Dual Infection with M. tuberculosis

According to the WHO, by the end of 2008 there were 34.3 million HIV/AIDS cases, 2.5 million new HIV infections, and 2 million deaths from AIDS. The HIV/AIDS population is at higher risk of TB infection. The probability of TB infection among HIV positive individuals is 30 times higher than that of people who are HIV (−) and PPD (+) (WHO 2011b, c; WHO 2009a). The possibility that HIV-positive individuals with latent TB will develop active TB is 20 times higher than that of HIV-negative people. TB can also speed up the progression of HIV infections. Over

the past 10 years, HIV transmission has accelerated the spread of TB in the world. According to data from the WHO, about 30 % of HIV infected individuals are also co-infected with *M. tuberculosis* and this proportion increases at a rate of 10 % each year. HIV infection and the AIDS pandemic is one of the main reasons for the global resurgence of the TB epidemic and it has made controlling TB extremely difficult (WHO 2009a; WHO 2011a; WHO 2010b).

Antiretroviral (ARV) drugs and anti-TB drugs can counteract each other. Rifampicin activates metabolic protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) of the cytochrome P450 liver enzyme system, leading to significant reduction in PI and NNRTI plasma concentrations. In addition, PI and NNRTI may enhance or inhibit enzyme systems and change the level of rifampicin in the blood. These types of drug interactions can increase the chances of treatment failure and drug toxicity for both ARV and anti-TB therapies (Manosuthi et al. 2009; L'homme et al. 2009; Nijland et al 2008). Because rifabutin is a weaker inducer of the cytochrome P450 liver enzyme system, the WHO has recommended rifabutin be used as a replacement for rifampicin when ARV and anti-TB therapies are co-administered (WHO 2010b; Khachi et al. 2009). However, the standardized effective dosage of rifabutin when used in combination with protease inhibitors has not been appropriately established, and the effective dosage in children is likewise unknown. The interactions between new anti-TB drugs and antiretroviral medicines require further research.

10.7.3 Treatment of Latent TB Infection

One-third of the world population has already been infected with *M. tuberculosis*, with most of those infected having latent infections. The purpose of treatment for latent TB infection is to prevent high-risk populations, such as close contacts of active TB cases and HIV-positive cases from developing active TB. Isoniazid preventive therapy of 6–9 months can prevent close contacts from developing active TB and reduce the probability of HIV-positive people developing active TB by 60 % (Spyridis et al. 2007; Woldehanna and Volmink 2006). Studies have shown that rifampicin treatment that lasts for 3–4 months also has some effect on latent TB infection (Ena and Valls 2005). Overall, however, the current preventive treatments are not optimal and the results are not ideal. New anti-TB drugs are needed to provide better latent TB treatment.

10.7.4 Treatment of Childhood TB

In TB high-burden countries, the incidence of TB in children is approximately 20 %, and TB in children is often very serious with high rates of hematogenous disseminated TB and tuberculous meningitis (Marais et al. 2004). Treatment of

childhood TB is difficult. The optimal doses of first-line anti-TB drugs are not entirely clear and internationally recommended dosages often fail to provide the adequate treatment. Clinical data treating children with second-line drug is lacking, and the safety of using ethambutol and fluoroquinolones to treat children has not been established (Marais et al. 2006; McIlleron et al. 2009). Therefore, it is necessary to find the optimal dosages of drugs for the treatment of children with TB, and it is imperative to develop new anti-TB drugs for this purpose.

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Chapter 11
The MDR-TB Epidemic in China: The Changing Landscape, Cause Analysis, Government Response, Current Status, and Future Aspects

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11.1 Introduction

The problems of drug-resistant tuberculosis (DR-TB) appeared soon after the medical application of anti-TB drugs. The most severe DR-TB problem in recent years has been multidrug-resistant TB (MDR-TB), in which the TB pathogen has become resistant to at least two of the most effective anti-TB drugs: isoniazid (H) and rifampicin (R) (WHO 2006). MDR-TB makes the TB disease not only difficult to treat but also creates new primary infections with a MDR-TB strain, thus making it possible for a MDR-TB epidemic (Wang 2006). At present, DR-TB, especially MDR-TB, has become the most serious challenge in the global fight against TB (WHO 2006). This chapter uses China as a case study to discuss the current MDR-TB epidemic and its possible causes, the government's strategy and specific measures to combat the epidemic, the various challenges and problems, and the future aspects of the MDR-TB prevention and control.

11.2 Current MDR-TB Epidemic in China

The current MDR-TB epidemic in China, like in many other developing countries in the world, is a very worrisome problem. According to the World Health Organization (WHO), the number of new MDR-TB cases annually in the world was 440,000 and, of these, 22.7 % (about 100,000) were reported in China (WHO 2010a).

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The MDR-TB rate in China is higher than the world average (WHO 2010b). In 2007–2008, the Chinese Ministry of Health conducted a National Tuberculosis Drug Resistance Survey and found that 8.3 % of the smear-test positive pulmonary TB patients had MDR-TB. Among new cases, 5.7 % had MDR-TB. Among retreatment cases, 25.6 % had MDR-TB. Table 11.1 shows the resistance spectrum of the surveyed MDR-TB cases along with their frequencies. All the MDR-TB strains were resistant to the most widely used anti-TB drugs (R and H) which had been the most effective treatment tools in the fight against the disease (Ministry of Health of the People's Republic of China 2010). Considering the availability and accessibility of all of these anti-TB drugs, the wide spectrum of MDR-TB in China is indeed worrisome for public health policy makers and officials, as well as public health workers and clinicians in the field.

While there were more females than males in the smear-test positive pulmonary TB patients who developed MDR-TB after having received their first time anti-TB drug treatment ($x^2 = 10.215$, $p = 0.001$), no statistical difference was observed between different age groups or between different regions in the country. In the smear-test positive pulmonary MDR-TB patients who had been previously treated, there were more female than male patients ($x^2 = 12.966$, $p = 0$), and a statistical difference was reported between ages ($x^2 = 27.772$, $p = 0$), with the group of ages 20~39 showing the highest rate. No statistical difference was seen between regions (Ministry of Health of the People's Republic of China 2010).

However, different regions in China do report different degrees of MDR-TB problems. In a WHO sponsored nationwide TB control project, 13 of the 31 provinces, autonomous regions, and municipalities in the country have participated

Table 11.1 Spectrum of multidrug-resistant TB strains (Ministry of Health 2010)

Drug resistance	% of total MDR-TB strains
H + R	12.97
H + R + E	8.48
H + R + S	23.94
H + R + OFX	1.50
H + R + KM	0.50
H + R + E + S	21.95
H + R + E + OFX	3.24
H + R + E + KM	0.50
H + R + S + OFX	2.99
H + R + S + KM	1.50
H + R + OFX + KM	0.25
H + R + E + S + OFX	12.47
H + R + E + S + KM	2.74
H + R + S + OFX + KM	1.00
H + R + E + S + OFX + KM	5.99
Total	100

Abbreviations: *H* isoniazid, *R* rifampicin, *E* ethambutol, *S* streptomycin, *OFX* ofloxacin, *KM* kanamycin

the drug resistance surveillance study since 1996. Data collected from 11 provinces showed that MDR-TB prevalence ranged from 3.5 to 16.9 % among all reported TB cases, with rates of 2.1 to 10.8 % among new smear-positive cases and 11.7 to 41.9 % among previously treated cases (WHO 2008a).

The MDR-TB epidemic in China has grown in recent years. A nationwide review study reported that the percentages of identified MDR-TB cases among TB patients had increased 3.84 times from 1985 to 2005 (Yang et al. 2010).

11.3 Possible Causes for the Current MDR-TB Epidemic in China

There are multiple possible causes for an expanding MDR-TB epidemic in China, including fundamental microbiology, errors in medical practice, and poor patient compliance. Microbiological adaptations are the nature of the evolution of any living organism, including the bacterial pathogens and their human hosts, and are somewhat unavoidable. In contrast, human factors such as clinical practice and poor patient compliance can be improved and errors can be corrected and prevented in future.

From a medical science point of view, drug resistance (or multiple resistances) acquired by the pathogen results from specific genetic mutations that enable it to survive in the presence of certain drugs. From a social science point of view, if a patient is prescribed an inadequate drug regimen, or fails to comply with a proper drug treatment plan, it is possible for the TB pathogens that have acquired drug-resistant mutation to gradually replace the original drug-sensitive strains (WHO 2008b). Therefore, accessibility to effective chemotherapy and high-quality public health services have been identified as the most important factors in reducing the chances of MDR-TB epidemics (Wang 2006).

In 2000, the fourth Chinese national epidemiological sampling survey of TB showed that only 12 % of the pulmonary TB patients received anti-TB drug treatment for their illness and only 4.3 % of the suspected TB patients actually went to a local TB prevention and control station to seek medical treatment (Wang et al. 2002). This is in spite of the central government's effort to provide DOTS (Directly Observed Treatment Short Course) nationwide, which by 2005 had reached 100 % coverage of all counties in the country.

In addition to the lack of public awareness of proper TB treatment, the incorrect usage of the available anti-TB drugs also contributed significantly to the MDR-TB epidemic (WHO 2006; Wang 2006). The anti-TB drug providers, who might have limited understanding of chemotherapeutic principles of the TB treatment due to the lack of proper medical training, could have prescribed incorrect drug(s) to TB patients, thus causing MDR-TB to develop (Wang 2006). In a report published by He et al. (2011), a survey of six local hospitals that specialized in TB treatment showed that only 18 % of the new patients and 9 % of retreatment patients were given the correct standardized TB drug treatment as required by the published national TB treatment guidelines.

Lack of patient compliance to the TB drug treatment plan is another major contributor to the rise of MDR-TB cases. Such medical noncompliance usually resulted from the lack of knowledge about the TB disease by patients in general and the lack of proper medical counseling by the medical staff and service providers. In 2006, a national survey found that only 75 % of the TB patients participated in the survey had the general knowledge of the correct course of an anti-TB drug treatment (Center for Disease Control and Prevention and Ministry of Health of the People's Republic of China 2008). The patients' noncompliance could also be a result of economic factors. For example, despite the fact that anti-TB drugs are provided by the government free of cost, some pulmonary TB patients might have financial difficulties to pay for additional auxiliary clinical examinations and medical expenses to treat severe drug side effects. Additionally, the regimen of taking multiple drugs over a long period of time can be difficult for patients to maintain.

Furthermore, currently there are no effective public health measures, if any, to manage those TB patients whose infection becomes MDR while undergoing standard anti-TB treatment. These new MDR-TB patients may spread disease by infecting others with their new MDR-TB strain, which in turn leads to new TB patients who are initially infected with MDR-TB and have little or no hope of receiving effective free medical treatment provided by the government for the limited kinds of expensive second-line TB drugs.

11.4 Government Plans and Measures to Combat the MDR-TB Epidemic in the Context of the National TB Prevention and Control

One of the most important government actions to control the spread of the MDR-TB epidemic in China has been to continuously improve the quality of the ongoing national programs to modernize the standard anti-TB drug treatment, thus reducing the numbers of MDR-TB that resulted from incorrect drug prescription, lack of treatment counseling, and medical noncompliance as described above (Tu 2006; WHO 2008b). In this regard, China may serve as a helpful case study for other countries or regions.

The Chinese national government started to modernize "The TB Supervision Chemotherapy Guidelines" nationwide in 1978. By 2005, all of the counties and districts in the country had reportedly implemented the National Strategic Plan for TB Control and Prevention, including the new standardized diagnosis, treatment, and management measures for newly identified smear-test positive pulmonary TB patients. Consequently, the rates of case identification and successful treatment achieved 80 % and 94 %, respectively, nationwide (WHO 2007). In the context of this, the National Strategic Plan for TB Control and Prevention, the new public health measures of preventing MDR-TB mainly include the following steps.

11.4.1 Increasing the National Budget for the TB Control and Prevention

In recent years, the central government has been increasing the national budget for TB prevention and treatment programs. There have been three 10-year national strategic plans for the TB prevention and control from 1981 to 2010, including the critically important national guidelines on the "National Tuberculosis Control Program (2001–2010)," which outlined the new modernized TB control strategy nationwide (Xiao 2011). The central government continued to increase the national budget for the TB prevention and control with a 40 million RMB ($6.25 million) fund directly allocated annually from the central government budgets. These funds were used for the purchase of anti-TB drugs, training of medical staff in modernized treatment and prevention practices, supervision of treatment counseling, and various public health awareness works. In 2004, the central government's spending on the TB program totaled up to 270 million RMB (Xiao 2011). As more development works of the TB prevention and control were implemented annually, the national TB budget continued to increase, and by the year 2010, the central government's spending on various TB prevention and control programs had increased to 570 million RMB (see Table 11.2). In the 10-year period from 2001 to 2010, the central government spent total of 3100 million RMB on improving effectiveness of clinical diagnosis of pulmonary TB patients, providing free anti-TB drugs, standardizing treatment compliance management, patient information tracking, and monitoring epidemic and health promotion work. Local government funds also showed an increasing trend yearly (Xiao 2011).

Increased spending by the central government has resulted in significant improvement in various key areas of both national and local TB prevention and controls, which in turn contribute to the prevention and control of MDR-TB nationwide. These key areas included:

(a) The implementation of the new standardized clinical diagnostics for pulmonary TB ensures the correct diagnosis for patients. Better trained medical staff and bet-

Table 11.2 National budget for the TB prevention and control (Xiao 2011)

Year	Budget (in million RMB)
2001	4000
2002	4000
2003	4000
2004	26,947
2005	26,554
2006	35,877
2007	48,918
2008	51,790
2009	53,654
2010	57,635
Total	313,375

ter management of drug treatment plans, combined with the registration of patient treatment records for better compliance, provide more effective drug treatment.

(b) Once anti-TB treatments are started, compliance counseling is provided by local TB clinics. Registered pulmonary TB patients are monitored with a periodic sputum sample check to insure early detection of treatment ineffectiveness or severe drug side effects that might affect patient's compliance with the prescribed drug regimen.

(c) Ensuring high product quality of the anti-TB drug supplies by the Chinese Food and Drug Administration (SFDA) with mandatory Good Manufacturing Practices (GMP) compliance for the production of all anti-TB drugs.

(d) Establishing the national TB disease surveillance system as well as other important infectious diseases. In 1982, China began to set up the TB disease monitoring system. By 2005, all the provinces in the country joined the internet-based national infectious disease reporting system which requires a quarterly update of TB disease surveillance and treatment monitoring. In the same year, the National Tuberculosis Management Information System became operational. The system has been optimized gradually with the medical science expert supervision and administrative supervision systems in combination with the international partners.

11.4.2 Specific Measures to Control the MDR-TB Epidemic

China uses the same set of specific measures for the MDR-TB control that has been used elsewhere in the world, that is, "DOTS-PLUS." Such measures were first proposed by the WHO in 1998 specifically for the control of MDR-TB (WHO 2006). The Chinese central government has since incorporated these specific measures into its own new modernized TB control plan to combat the growing MDR-TB epidemic in the country. The following is a brief description of these specific measures:

(a) New national funds were specifically established, including the new medical insurance fund, the MDR-TB epidemic monitoring fund, and the relief policy on the diagnosis and treatment of patients with MDR-TB. These new funds have significantly improved the local public health systems nationwide and enabled them to establish the new TB control services. These services include the local general hospitals, the TB special clinics, and the TB prevention and control institutions, all of which have basic TB clinical laboratory capability and are part of the National Center for Disease Controls networks. The new national fund also made it possible to improve the national important infectious disease registration system. On the basis of the Tuberculosis Management Information System established by the central government, the online registration report modules now include the records of MDR-TB diagnosis and treatment histories (Huang et al. 2011). As described in the following sections, these new funds and new infrastructures are designed to play critical important roles in controlling the spread of MDR-TB in China.

(b) To detect MDR-TB early by using the newly acquired clinical laboratory capacities nationwide such as the high-quality standard sputum culture system combined with the sensitive in vitro drug-resistant assays. Once a TB patient is diagnosed with MDR-TB, he or she can receive a second-line anti-TB drug regimen with special care, thus reducing further spread of MDR-TB. If necessary, some of these patients can be hospitalized and even isolated for better protection of his or her families and close communities. In regions with sufficient resources, all the smear-test positive TB patients diagnosed in general hospitals or TB special clinics are required to be screened for MDR-TB (Mi et al. 2011). Such MDR-TB screening is especially important for chronic pulmonary TB patients with bacterial discharge or close contacts with known MDR-TB patients. Smear-test positive pulmonary TB patients who are being retreated with anti-TB drug treatment and the first time TB patients remaining smear-test positive after 3 months of anti-TB drug treatment are also required to be tested for the presence of MDR-TB.
(c) To provide a more effective second-line anti-TB drug regimen to treat MDR-TB based on the results of drug-sensitive tests. For TB patients who have developed severe side effects that could result in noncompliance with the standard anti-TB drug treatment for the first time, alternative drug regimens should be considered. In order to ensure the qualities of the anti-TB drugs, the drug manufacturers are required to follow strict regulatory guidelines as issued by the Chinese FDA.
(d) To strictly follow the DOT protocols in all inpatient and outpatient treatments for MDR-TB. Regular medical counseling, including psychological counseling, is required to help the patients to complete their prescribed course of treatment with self-confidence, thus improving patients' compliance and reducing the probability of developing more severe forms of MDR-TB.
(e) To protect medical professionals and public health workers from being infected by MDR-TB patients in hospitals, TB clinics, and TB prevention and control stations. Identified MDR-TB patients are required to be assigned to separate hospital wards with a strict set of environmental disinfection procedures such as proper ventilation of the rooms, disinfection by ultraviolet irradiation, and periodic surface disinfections.

11.5 Current Status of the MDR-TB Control in China

China is a huge country with more than one billion people who reside in 22 provinces, 5 autonomous regions, and 4 municipalities. The differences between these provinces, regions, and municipalities are very significant in their cultures, living standards, disease burdens, social economic status, and other factors. These differences readily affect the MDR-TB control efforts and obviously make any national disease control program very difficult to manage successfully. The following sections describe various problems and challenges facing the national MDR-TB program.

11.5.1 Implement the International Standard MDR-TB Surveillance and Registry System Nationwide

In 1996, China began to implement the global TB drug resistance surveillance project as directed and supported by WHO and The International Union Against Tuberculosis and Lung Disease (The Union), which included the monitoring of MDR-TB in different provinces. To date, the project has been carried out in several of the 31 provinces, autonomous regions, and municipalities in the country. These include the provinces of Guangdong, Henan, Hubei, Liaoning, Shandong, Zhejiang, Hunan, and Heilongjiang; the autonomous regions of Inner Mongolia and Xinjiang; and the municipalities of Chongqing, Beijing, and Shanghai. Fund-raising efforts to set up the MDR-TB monitoring projects are actively carried out in the six additional provinces of Yunnan, Shaanxi, Jilin, Fujian, Guangxi, and Sichuan. This leaves 12 provinces (autonomous regions or municipalities) in the country where an international standard MDR-TB monitoring system needs to be established.

The Chinese Ministry of Health conducted a national baseline survey of TB drug resistance in 2007–2008. This survey included 70 survey stations distributed in all 31 provinces, autonomous regions, and municipalities in the country, which covered an estimated population of 47 million out of the 1.3 billion Chinese at that time. The survey collected sputum samples from a total of 4600 cases of the smear-test positive TB patients using the stratified cluster sampling method, including 3514 cases of the first time smear-test positive patients and 1086 cases of TB patients for retreatment (Ministry of Health of the People's Republic of China 2010). This national survey revealed the Chinese TB drug resistance baseline information, including the rates of drug resistance and drug resistance spectrum, resistance causes, and provided a scientific basis for the formulation and implementation of Chinese TB-resistant control strategies and measures (Ministry of Health of the People's Republic of China 2010).

11.5.2 Improve the Existing National TB Registry Information Management Systems by Gradually Adding Routine Monitoring of MDR-TB

In 2005, the Chinese Center for Disease Control and Prevention (China CDC) started to add the current TB disease registry information management system on the basis of the previously established national network of reporting systems for infectious diseases. This important addition has enabled all of the TB hospitals and clinics nationwide to manage their local and regional TB prevention and control activities and new disease information electronically using Internet. Through the establishment of this new system, real-time monitoring of the TB epidemic nationwide became possible, and patient registration and treatment prognosis could be reached in a timely manner. However, such existing TB registry information

management system was created to deal with regular TB (not MDR-TB), patient registration, anti-TB drug treatment follow-up, and the treatment management and planning activities for the national and local CDC.

Therefore, there had been an urgent need for a similar real-time registry information management system to monitor the spread of MDR-TB epidemic in the country, On April 1, 2011, an internet-based MDR-TB disease information management system was launched nationwide. This included MDR data collection, quality control, and statistical analysis reports. Using this system, local and regional MDR-TB disease information can also be quickly transmitted among the local TB prevention stations, community TB treatment clinics, and regional TB hospitals between neighboring counties, different provinces, and with the central government in Beijing. This nationwide disease information sharing network makes it possible to track the spread of MDR-TB and manage and follow the treatment of the identified MDR-TB patients.

11.5.3 Launch the Pilot Projects on MDR-TB Control That Can Be Followed by Nationwide Expansions

Dealing with MDR-TB is much more demanding than drug sensitive TB with respect to accurate clinical laboratory diagnosis, appropriate drug regimen selection for treatment, and patient compliance with the entire course of a specifically chosen treatment. Identifying and treating MDR-TB patients also demands much higher quality medical care provided by medical staff and public health workers at all levels, which of course in turn demands much more financial funding to make this possible. Considering all these potential difficulties and obstacles, the 2001–2010 National TB Control Program requested that the national and local CDC launch pilot studies for annual implementation on the new MDR-TB control projects between 2006 and 2010. These pilot projects are collectively named as "Multidrug Resistant Tuberculosis Treatment Management and its Gradual Promotion" program (Ministry of Health of the People's Republic of China 2011).

One of these pilot projects was the Chinese Fifth Round Global Fund TB Project, which focuses on dealing with the challenges of identifying and treating pulmonary MDR-TB patients, the spread of TB in the increasing migrating labor population in the country, and the TB/HIV co-infections. In October 2006, this pilot study was initiated in the city of Wuhan in Hubei province and in the city of Shenzhen of Guangdong Province.

Throughout this pilot project, a new disease control operational policy was put in test. The new policy calls for the "City to Declare, Province to Evaluate and Recommend, and the Nation to Inspect and Approve" of a proposed MDR-TB treatment management plan. Such a new policy laid a structural foundation for a regional MDR-TB control work, in which a city acts as a control information management center, a county acts as a drug treatment and information management hub, and an individual community acts as a base unit to perform all the functions. It also built up

a cooperation mechanism for all local TB clinics, regional TB hospitals, and different levels of CDC stations to carry out all necessary inpatient and outpatient drug treatment combination therapies in compliance with DOT. During the pilot study, the classical drug sensitivity tests were used for screening the TB patients with chronic TB symptoms, or with close contacts with a known MDR-TB patient, or tested as the smear-test positives after receiving the standard anti-TB drug treatment at the end of 3 months. The newly diagnosed MDR-TB patients were then treated with the proposed standard second-line anti-TB drug regimens: a 6-month treatment of Pyrazinamide (Z), Kanamycin (Km), Levofloxacin (Lfx), Prothionamide (Pto), and P-aminosalicylic acid (PAS), then 18 months of PAS (6 Z Km LfxPto PAS/18 PAS). All the second-line drugs were imported through the Global Drug Facility (GDF) and were freely provided to the confirmed MDR-TB cases. Once a second-line drug treatment for MDR-TB is started, the pilot model system provides the patient with a follow-up management plan. This plan may include hospitalization for inpatient clinical care, outpatient management with DOT and other community services, or a combined approach of inpatient and outpatient treatments. Patients are treated in a designated TB special hospital for the first 2 months, then return to their own residential communities for outpatient treatment care in TB clinics with DOT services, and finally return to the TB special hospitals where the treatment started for the follow-up treatment evaluation. The evaluation is performed in compliance with the regulations by the national MDR-TB control plan.

In recent years, the increasing TB control funds from the central, regional, and local governments together with the international funds from The Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund), the above-described pilot projects for MDR-TB control have been gradually expanding to more and more cities in China. By 2011, similar projects had been started in 41 cities in 12 different provinces nationwide. By 2012, the pilot projects expanded to 67 cities in 24 provinces. In 2013, the pilot projects were expanded to a total of 81 cities in 24 provinces.

While the geographic areas for the MDR-TB patient treatment have been gradually expanding, the qualities of the medical services for the MDR-TB treatment have also been continuously improving. The specific goals for the proposed quality improvement include (a) to provide the MDR-TB clinical laboratory tests for all the smear-test positive pulmonary TB patients in the covered areas; (b) to provide frequent drug resistance monitoring services to all the patients receiving the second-line drug treatment for MDR-TB in the areas; (c) to provide necessary TB special hospital beds, transportation assistance to the needy outpatients, essential nutritional aids, and psychological counseling support services for all the diagnosed MDR-TB patients in the areas; (d) to offer special helps to HIV-infected pulmonary TB patients who are tested negative for smear-tests but need to be tested with more expansive sputum culture tests and the possible follow-up drug-resistant tests if tested positive by the culture tests; and finally, (e) to introduce the new diagnostic testing tools into local hospitals and clinics by setting up the “demonstration laboratories for MDR-TB diagnosis and treatment” in each province in the project covered areas and undertaking the initial provincial hospital laboratory testing demonstrations and the city-level clinical treatment provider demonstrations.

11.5.4 Combat the MDR-TB Epidemic with Advanced Medical Researches with New Diagnosis and Treatment Tools

In order to effectively control the growing MDR-TB epidemic in China, TB clinicians and public health workers in the country should have access to the most advanced clinical diagnosis tools as well as the best available second-line anti-TB drugs. From the government point of view, it is essential not only to provide the necessary financial resource and coordinated national disease control policies to combat MDR-TB but also all the best advanced biomedical tools to ensure the success. For instance, the traditional practice for MDR-TB diagnosis, which has been used commonly in China until very recently, involves patient's sputum collecting and culturing, followed by drug resistance assays or direct sequencing of the TB pathogen isolated from the sputum samples. If a second-line drug treatment is considered, additional drug sensitivity tests may be required, too. Such a lengthy series of clinical laboratory procedures usually takes about 6–8 weeks or longer. In 2010, the Chinese FDA approved two new TB diagnostic products, the Tuberculosis Drug Resistance Detection Array Kit and the Mycobacteria Identification Array Kit (both from CapitolBio, Beijing), that significantly reduce the time requirement to achieve a confirmed test result. Both products are based on advanced DNA microarray methods and were developed by the National Engineering Research Center for Beijing Biochip Center with the direct financial support from the Ministry of Health and the Ministry of Science & Technologies (Wang et al. 2010). These new TB diagnostic products are much faster and have a much higher throughput than the traditional detection methods, thus allowing rapid identification of various drug resistance TB strains, including the 17 MDR-TB strains that had been most commonly reported in China. Available data from the independent clinical evaluation studies showed that the MDR-TB clinical diagnosis time has been shortened to 6 h and the assay specificity can be clinically confirmed with as high as 99 % accuracy in 1700 clinical samples (Chinese Medicine Biological Technology Association of Biological Chip Branch 2011). In these studies, the DNA microarray-based new TB diagnosis products shortened the detection time for the rifampicin and isoniazid resistance from 8 weeks to 6 h. A clinical trial performed by an independent third party showed 100 % consistency with the old time-consuming method of DNA sequencing. The sequencing results of the isolated MDR-TB strains confirmed 92 % of these rapid tests for the rifampicin resistance and 78 % of the isoniazid resistant (Guo et al. 2009). Larger scale of applications of these new products may significantly improve the effectiveness of the current MDR-TB control projects nationwide.

The Ministry of Health had closely collaborated with the Bill & Melinda Gates Foundation to promote wider clinical applications of new MDR-TB diagnostic products in China. The central government has promoted scientific collaborations on MDR-TB control between TB researchers in medical research institutions, clinicians in TB special hospitals, and public health workers in the local CDC stations. Other national research areas also involve the health care insurance companies,

Table 11.3 Some ongoing national studies on MDR-TB

Research topic	Institution
Multiple Drug Resistant Pulmonary Tuberculosis Epidemic and Treatment Strategies	National Center for TB Control and Prevention, China CDC
A Retrospective Study of the Cause and Outcome of Multiple Drug Resistant Tuberculosis	National Center for TB Control and Prevention, China CDC
The Investigation of Second-line Anti-tuberculosis Drug Usage and Drug Sensitivity Testing	National Center for TB Control and Prevention, China CDC
The Infection Status and Influential Factors for MDR-TB Close Family Contacts	National Center for TB Control and Prevention, China CDC
The Study for Comprehensive Treatment of Multidrug-resistant Tuberculosis	Guang Dong provincial TB dispensary
The Study of a Clinical Occurrence Warning Model for Drug Resistant Tuberculosis Research	National Center for TB Control and Prevention, China CDC
New Technology Platform Research for Tuberculosis Infection Control	National Center for TB Control and Prevention, China CDC

government funding agencies, alternative fund-raising mechanisms, and the use of third parties for supervision and payment of detecting and treating MDR-TB.

Some of the ongoing national studies on MDR-TB are listed in Table 11.3. These studies are expected to further improve the central government's ability to control the MDR-TB in the country.

11.5.5 Provide the National Guidelines for MDR-TB Control Policies and Medical Practices

As the first-line anti-TB drugs are still the most powerful tool in the prevention and control of the current TB pandemic in China, it is very important for clinicians as well as TB patients to use these drugs correctly in order to maintain their effectiveness and prevent the appearance of MDR-TB. The China CDC in 2008 joined with the Chinese National TB Prevention Association and the Chinese Medical Association to publish the "Handbook for the Use of Anti-tuberculosis Drugs" (Chinese Center for Disease Control et al. 2008) which described the characteristics, principles, methods, and adverse reactions of each anti-TB drug, as well as how to make the best combination to reach the best treatment effect.

Then "The Handbook of Chinese Tuberculosis Control and Prevention" was subsequently published in 2010, which elaborated on the TB prevention and control, especially in the different environments and populations. The handbook also outlined TB prevention and control in China from the governmental point of view, thus providing detailed guidelines on the organizational management structure, management measures, working environmental and engineering controls for public health workers' personal protections. The handbook was specially designed to be applicable for all levels of governmental agencies on TB prevention and treatment institutions,

hospitals, and health organizations. The book offered guidelines for management personnel, the medical personnel of the medical and health institutions on how to control the TB infection within medical institutions, the crowd gathering places, public places, and family environments with pulmonary TB patients (Wang et al. 2010).

The first national guidelines dealing specifically with MDR-TB for public health workers and TB clinicians in the country was the "Multidrug-resistant Tuberculosis Chemotherapy Views (for Trial Implementation)" written and published by the Chinese National TB prevention Association in 2002. Then in 2009, with the new knowledge and lessons learned during the previous trial period, the book was revised and renamed "Treatment Guidelines for Drug resistant Tuberculosis Medicine," which included the contents from the "Drug-resistant Tuberculosis Planning Guide—2008 Update Edition" and elaborated on the determination and adjustment of then commonly used MDR-TB drug treatment schemes and how to deal with adverse reactions to the treatments (Chinese Antituberculosis Association 2010).

Then in 2010, the National Bureau of Disease Control & Prevention and the Department of Medicine of the Chinese Ministry of Health, together with the China CDC, issued the current national policy document, "The Management Guideline of Multi-drug Resistant Pulmonary Tuberculosis." The new national guideline is not only in consistent with "The Management Guideline of Drug Resistant Tuberculosis" as produced by WHO in 2006, it also includes the special experiences and lessons from all of the pilot projects during the previous trial years in China, thus becoming a practically useful guidebook to all TB clinicians and public health workers at all levels of the government agencies involved in the country's fight against MDR-TB.

At the national public health policy level, the prevention and control of MDR-TB had been written into the "National TB Control Program (2001–2010)" for the first time. It was subsequently issued again at the national level as the 2006–2010 implementation plan. The other policy-oriented documents and technical supporting papers issued by the central government also include the following (Ministry of Health of the People's Republic of China 2011):

(a) Developing framework and implementation planning of national MDR-TB prevention and control work
(b) Performing a pilot study on MDR-TB treatment management
(c) Developing TB drug resistance surveillance
(d) Strengthening TB laboratory biosafety management; improving laboratory working conditions; and gradually meeting the required biological safety standards
(e) Taking a step-by-step approach to initiate the new modernized sputum culturing technologies or to replace the old methodology gradually with the new one
(f) Expanding the clinical laboratory testing capacities to include the best available TB drug sensitivity experiments

At present, the China CDC has drafted a new policy document named "The Framework of the Nationwide MDR-TB Prevention and Control." Its main contents include preventing the occurrence of drug resistant TB, strengthening the new TB clinical laboratory network construct, identifying and monitoring MDR-TB,

developing the new functional roles of TB special hospitals and local clinics in administering the new standardized second-line drug treatment for MDR-TB patients, promoting public health awareness campaigns about prevention of the spread of MDR-TB, and other related new public measures.

11.6 The Future Prospect for MDR-TB Prevention and Control in China

In recent years and at present, the problem of having to deal with drug-resistant TB in China has become increasingly prominent. If not effectively controlled, the current MDR-TB epidemic will certainly be growing significantly in the coming years and will make the TB prevention and control task even more challenging.

The Chinese Leadership has been taking the threat of MDR-TB very seriously. In April 2009, public health ministers around the world from countries with the greatest burden of drug-resistant TB gathered in Beijing and endorsed a Call for Action on the prevention and control of MDR-TB and Extreme Drug-Resistant TB (XDR-TB; WHO 2009). A month later, the 62nd World Health Assemblies in Geneva passed a similar resolution sponsored by the Chinese delegation. During the 2009 Beijing Ministerial Conference on MDR-TB, the current Chinese Premier Li Keqiang, then the vice premier in charge of the national health, together with the WHO director and the president of the Gates Foundation, declared that the Chinese government will work closely with the international community to strengthen the prevention and control of MDR-TB in China in the coming years (Chen 2009). The details of this plan focused on achieving the following specific goals:

(a) By 2015, more than 80 % of the national TB clinical laboratories should be able to carry out the new sputum cultivation works, and 100 % of the regional TB clinical laboratories should be able to conduct the TB drug sensitivity tests. By then, all of the provincial clinical TB laboratories should also be able to meet the rapid TB strain identification requirements and each major city in the country should have established a centralized clinical laboratory unit to be capable of providing MDR-TB clinical diagnosis.
(b) By 2015, up to 60 % of the identified MDR-TB patients in the country should be able to have access to drug-sensitive tests, second-line anti-TB drug treatment in compliance with DOTS, and the standardized follow-up medical services, If successful, these measures should reduce the MDR-TB incidences, death rate, and the disease transmission in the country.
(c) Domestic anti-TB drug manufacturers should receive more support in order for them to supply the country with the high quality first-line and second-line anti-TB drugs. In order to support other countries in need, these qualified Chinese drug manufacturers should also acquire all the necessary international quality certifications. More specifically in the near future, cycloserine and p-aminosalicylic acid granules should become available in order to enrich the

current second-line anti-TB drug choices. The development, assessment, and promotion of new diagnostic tools should be actively promoted.

(d) By 2015, the medical staff should be trained on detecting and treating MDR-TB in order to train personnel and build up a steady TB prevention and control team. MDR-TB prevention and control demands higher technical requirements and a longer course of treatment. In order to achieve a complete cure, the staff needs to be highly responsible and devoted to anti-TB work. In the control process, especially during the treatment, changing staff often will affect the patient's treatment and lead to new multidrug-resistant patients. The human resources should be strengthened on diagnosis, treatment, and prevention of laboratory management, and gradually form an anti-TB diagnosis, treatment, and prevention management team)

(e) There have been no new anti-TB drugs since the 1960s in China. The development of new first and second-line anti-TB drugs or regimens, with a shorter course of treatment and easy for a patient to take regularly, with fewer and milder side effects, will become more and more desirable for the fight against MDR-TB. As the issue of cost effectiveness of treating MDR-TB will certainly become more and more important for the government, local communities, and patients, new research and development of new effective prophylactic vaccines will continue to be the hope of a new era of controlling MDR-TB in China and in the rest of the world.

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Chapter 12
Treatment of TB and HIV Coinfection

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While the incidence of human immunodeficiency virus infection (HIV) and acquired immunodeficiency syndrome (AIDS) has been decreasing globally, the rate of tuberculosis (TB), especially drug-resistant tuberculosis (DR-TB), is still relatively high. The incidence of tuberculosis and HIV coinfection (TB/HIV) increases year to year, and the difficulties and challenges of global TB control have caused widespread concern among health professionals.

12.1 Trends of TB/HIV

The United Nations AIDS organization (UNAIDS) reported that more than 60 million people have been infected and nearly 30 million HIV/AIDS patients have died worldwide since HIV/AIDS became an epidemic (UNAIDS 2010). In 2009, there were more than 33.3 million cases of HIV/AIDS, an increase of 2.6 million new HIV infections. About 1.8 million patients died of AIDS worldwide. More than 50 % of these HIV-infected persons were located in sub-Saharan African countries. In China, since the first case of AIDS appeared in 1985, the reported number of cumulative HIV infections and AIDS patients by the end of October 2009 was 319,877 cases leading to 49,845 deaths. In 2009, the Ministry of Health of China, the UNAIDS, and the World Health Organization (WHO) collaborated to evaluate the epidemic of AIDS in China. They estimated that by the end of 2009, China would have about 740,000 people living with HIV, including 48,000 newly infected and 105,000 AIDS patients.

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According to WHO statistics, more than 30 % of HIV-infected individuals are coinfected with *Mycobacterium tuberculosis*, with an annual increase of 10 %. In 2006 alone, there were 710,000 people newly infected with TB/HIV which lead to 230,000 deaths (Wright and Zignol 2008). In China, TB/HIV patients account for 15.9 % of HIV/AIDS patients and the number is growing (Lu et al. 2007). Until recently, there was little epidemiological data available in China and worldwide regarding the morbidity of HIV patients coinfected with drug-resistant (DR), multidrug-resistant (MDR), or extensive multidrug-resistant (XDR) TB. In South Africa, 40 % of MDR-TB patients are coinfected with HIV, an annual increase of 4000 MDR-TB/HIV cases (Gandhi et al. 2006). In India, the incidence of MDR-TB/HIV is 4.4–5.9 % among the HIV-infected patients, while a rate of 26.4 % was found in Latvia. The mortality rate of MDR-TB/HIV is as high as 41–72 %.

12.2 Pathogenesis of TB/HIV

Both TB and HIV have suppressive effects on the host immune system; specific interplays between the infections make coinfection particularly dangerous.

12.2.1 Pathogenesis of HIV

HIV mainly infects $CD4^+$ T cells, mononuclear phagocytes, B lymphocytes, microglia, and bone marrow stem cells. After HIV enters the human body, its glycoprotein (gp120) located on its surface membrane combines with the host's $CD4^+$ receptor located on the surface of some T lymphocytes. This allows HIV to enter the cell. Then HIV's single-stranded RNAs are transcribed into double-stranded deoxyribonucleic acid (DNA) by reverse transcriptase and subsequently integrated into the DNA of the host cell. This eventually causes the number of $CD4^+$ T lymphocytes to progressively decline. Surviving $CD4^+$ T lymphocytes have reduced function, leading to declines in cellular immunity. During the early stage of HIV infection, there is a reduction of natural killer cells, which are a first line of defense against newly malignant cells. HIV can also infect mononuclear phagocyte cells, leading to their dysfunction and decline. As immunity declines, serious concurrent opportunistic infections can occur.

12.2.2 The Influence of HIV on M. tuberculosis *Infection*

People infected with *M. tuberculosis* have a 5–10 % chance of developing active TB in their lifetime. However, people coinfected with *M. tuberculosis* and HIV have a 50 % chance of developing TB in their lifetime. Cell-mediated immunity plays a

major role in controlling *M. tuberculosis* infection. HIV infection reduces the number of $CD4^+$ T cells and the cytokines released by T lymphocytes, such as interferon-γ (IFN-γ) and interleukin-2 (IL-2). After HIV-positive patients are exposed to *M. tuberculosis*, INF-γ is reduced, thus reducing the responsiveness of T helper 1 (TH1) cells. This reduced immunity leads to TB in three ways: primary infection, endogenous recrudescence, and exogenous reinfection.

Additionally, HIV infection has a certain relationship with the incidence of DR-TB, including MDR-TB and XDR-TB. The exact mechanism or influence factors are not known. The occurrence of MDR-TB/HIV is possibly related to acquired rifampin resistance and gastrointestinal malabsorption caused by anti-TB drugs and/or poor patient compliance (Gandhi et al. 2006). It may also be related to acquiring isoniazid resistance caused by using isoniazid in TB preventive therapy.

12.2.3 The Impact of M. tuberculosis *on HIV Infection*

In recent years, studies have found that after HIV patients are infected with *M. tuberculosis*, the secretion of inflammatory cytokines declines in vivo. This interferes with the immune system's ability to stop HIV from invading target cells (Toossi et al. 2001). After the TB infection, T lymphocytes are activated and cytokines they release can significantly increase the amount of HIV proviral transcriptions, accelerating the proliferation of virus and promoting the progression of disease. When the body is infected with TB, T Helper 2 (TH2) cells are induced, which can suppress the resistance of cells to viral infections. In addition, the number of CXCR4 receptors found on the surface of dendritic cells (DCs) increases, enhancing HIV infection of DCs. Thus, *M. tuberculosis* infection plays a catalytic role in several key stages of HIV infection: target cell binding, transcription, latency, and the spread of provirus.

12.3 Clinical Features of TB/HIV

AIDS patients experience constitutional symptoms including fever, night sweats, anorexia, weight loss, and chronic diarrhea. Examination can show general lymphadenectasis and hepatosplenomegaly, also known as AIDS-related syndrome.

The clinical manifestations of HIV/AIDS may vary according to the stage of infection throughout a patient's physiology, and are often accompanied by opportunistic infections. With respect to the respiratory system, 70–80 % of AIDS patients repeatedly experience *Pneumocystis* pneumonia (PCP). *M. tuberculosis*, nontuberculous mycobacteria (NTM), *Candida*, and *Cryptococcus* may also cause lung infection, leading to chronic cough, fever, cyanosis, and hypoxemia. In the nervous system, opportunistic infections, cancer, sepsis-related encephalopathy, and primary HIV infection can cause neurological symptoms such as headache, epilepsy,

dementia, cerebral paralysis, limb paralysis, and spastic ataxia. As for the digestive system, the patients show thrush, esophagitis or ulceration, odynophagia, retrosternal burning sensation, diarrhea, weight loss, and liver enlargement. These mainly relate to opportunistic infections and Kaposi sarcoma. With respect to the mucous membranes of the skin, *Candida* stomatitis and oral hairy leukoplakia are the common symptoms. Inflammatory skin disorders can be caused by condyloma acuminatum and psoriasis. When Kaposi's sarcoma invades the mucous membranes of the skin, purple or dark blue infiltration spots or nodules appear. In addition, patients can show flocculent white eyes.

12.3.1 Clinical Manifestations of TB/HIV

Signs and symptoms of TB in HIV-infected patients are similar to those in the HIV-negative patients. However, its clinical features depend on the degree of immune suppression. For example, when TB develops during the early stage of HIV, its signs and symptoms are similar with those of HIV-negative patients. If the TB develops at the late stage of HIV, weight loss, dry cough, and fever are the common symptoms, while sputum and hemoptysis are rare to see. This could be due to the fact that HIV-positive patients rarely show emptiness, inflammation, and bronchial irritation.

12.3.1.1 Extrapulmonary TB

HIV patients with lymph node TB always have an attack with acute lymph node inflammation. The histological features depend on the degree of immune deficiency. The lymph nodes of mildly immune deficient patients usually only have acid-fast stain-negative caseous necrosis. In severely immune deficient patients, lymph nodes show large acid-fast bacilli, but not associated with a cellular response. The clinical manifestations of HIV-positive patients with tuberculous effusion and tuberculous meningitis are similar to HIV-negative patients. When HIV-infected patients are also infected with hematogenous disseminated TB, they have severe immune suppression because of advanced cachexia. The lack of abnormal chest X-ray findings makes the diagnosis of the hematogenous disseminated TB difficult.

12.3.2 Laboratory Tests

In general laboratory tests, TB/HIV patients may show a reduction in white blood cells, hemoglobin, red blood cells, platelets (to varying degrees), as well as increased serum transaminase, positive urine protein, and renal dysfunction. In immunological tests, the total number of T lymphocytes decreases, and the CD4/CD8 ratio is $\leq$1.0. Immunoglobulins, specifically β2 microglobulin, increase. With *M.*

tuberculosis coinfection, the interferon-γ release assay (IGRA) or enzyme-linked immunosorbent assay (ELISA) is positive.

12.3.2.1 Pathogen Detection: HIV

Anti-HIV antibodies in serum, urine, saliva, or cerebrospinal fluid can be detected by ELISA. ELISA can also be used to detect p24 antigen in serum. Flow cytometry can be used to detect HIV-specific antigens in blood samples. HIV can be isolated from plasma, mononuclear cells, and cerebrospinal fluid in HIV-infected patients, but due to procedure complexity, these techniques are mainly reserved for research purposes.

12.3.2.2 Pathogen Detection: TB

In TB/HIV patients, the positive rate of sputum smear acid-fast stain and culture may be affected by the patient's immune system function and status of lung lesions. PCR can be used to detect the specific target sequence in *M. tuberculosis* nucleic acid in sputum and blood, but the assay's sensitivity and rate of false positives are also affected by the patient's immune status.

12.3.3 Pulmonary Imaging

The pulmonary imaging performance of TB/HIV patients depends on the degree of immune function. When immune function is moderately impaired, the imaging shows previous leaf or double leaf infiltration, emptiness, and pulmonary fibrosis. When immune function is severely impaired, the imaging shows ousted interstitial pulmonary infiltration, intrathoracic lymphadenopathy enlargement, and no emptiness.

12.4 Diagnosis and Identification of TB/HIV

12.4.1 Diagnosis

HIV testing should be considered when the patient presents a combination of the following information:

Past history: sexual transmitted infections (STI), herpes zoster infections, recent or recurrent pneumonia, severe bacterial infections (sinusitis, sepsis, purulent metritis), recent anti-TB treatment.

Symptoms: weight loss (more than 10 kg or more than 20 % of original weight), diarrhea (over 1 month), retrosternal pain when swallowing (esophageal candidiasis prompted), burning sensation in the feet (peripheral sensory neuropathy).

Signs: herpes zoster scars, obvious itching from maculopapular rash, Kaposi's sarcoma, symmetrical whole body lymph node enlargement, oral candidiasis, angular cheilitis, oral leukoplakia, necrotizing gingivitis, huge canker ulcers, long-lasting and painful genital ulcers.

12.4.1.1 Laboratory Tests

Common HIV tests detect HIV antibodies in serum or plasma. Detection of virus, p24 antigen, and/or viral nucleic acids and culturing can also be used to make a diagnosis. For areas where HIV testing cannot be performed, the WHO recommends an AIDS diagnosis if adults have two of the main manifestations and one of the secondary manifestations listed below.

Main manifestations: more than 10 % of weight loss and more than a month of chronic diarrhea and long-term fever.

Secondary manifestations: more than a month of persistent cough, generalized pruritic dermatitis, herpes zoster, oropharyngeal candidiasis, generalized lymphadenopathy, chronic progressive or disseminated herpes simplex virus infection.

12.4.1.2 The Clinical Stages of HIV Infection

The typical HIV-infected patient experiences three stages: the acute phase, asymptomatic phase, and the AIDS period. The WHO formulated a clinical staging based on the clinical standards (Table 12.1).

12.4.1.3 Diagnosis of TB/HIV

HIV/AIDS patients can be diagnosed with TB/HIV under the following conditions:

- Patient has TB-related clinical manifestations and typical imaging characteristics.
- Patient has positive results from sputum acid-fast stain, sputum culture, and/or blood PCR.
- Patient serum is TB antibody positive by IGRA or ELISA. Positive IGRA or ELISA results are especially important for TB diagnosis in HIV patients whose bacteria culture tests are negative.

The patient can be diagnosed with TB/HIV (including extrapulmonary TB) when the following manifestations appear:

Table 12.1 Clinical stages of HIV infection (Harries et al. 2004)

Stage 1	Asymptomatic or with persistent generalized lymphadenopathy
	Behavior classification 1: asymptomatic, normal activity
Stage 2	<10 % weight loss, mild mucosal and skin lesions (e.g., oral ulcers, fungal nail infections), herpes zoster occurring for nearly 5 years, repeated upper respiratory tract infection
	Behavior classification 2: symptomatic, normal activity
Stage 3	>10 % weight loss, >1 month of unexplained chronic diarrhea, >1 month of unexplained long-term fever, oral candidiasis (thrush), oral leukoplakia, pulmonary TB, severe bacterial infections (pneumonia, purulent myositis)
	Behavior classification 3: less than 50 % bed days in the last month
Stage 4	HIV wasting syndrome (>10 % weight loss, >1 month of unexplained chronic diarrhea, chronic weakness, and >1 month of unexplained long-term fever), *Pneumocystis* pneumonia (PCP), cerebral toxoplasmosis, >1 month of *cryptosporidium* diarrhea, extrapulmonary cryptococcosis, CMV infections in organs in addition to the liver, spleen, lymph, >1 month of mucocutaneous herpes virus infection or visceral herpes virus infection, progressive multifocal leukoencephalopathy, any fungal infection, atypical mycobacterial disease, non-typhoid *Salmonella* septicemia, pulmonary TB, lymphoma, Kaposi's sarcoma, HIV encephalopathy. In addition to HIV, clinical findings of cognitive or movement disorders affecting daily life for several weeks/months, and/or other concurrent diseases or conditions that cannot be explained
	Behavior classification 4: more than 50 % bed days in the last month

- Typical clinical manifestations of TB
- Positive result from acid-fast stain of body fluids (pleural and peritoneal effusions, cerebrospinal fluid, etc.), TB bacterium culture, and/or PCR
- Positive result from serum TB antibody test, IGRA, or ELISA
- Positive PPD test
- Lymph node biopsy shows characteristic pathological changes of TB, etc.

In TB patients, the possibility of TB/HIV should be considered and patients should be tested for HIV when the following symptoms appear:

- Thrush, significantly enlarged systemic lymph node, lymphopenia, difficulty breathing, etc.
- Rapid progress to TB, multiple pulmonary nodules
- Other concurrent opportunistic infections (e.g., fungal infection)

An HIV diagnosis should be based on positive HIV antibody test with a confirmation test.

12.4.1.4 Diagnosis of DR-TB/HIV

The WHO has called for all TB/HIV patients to undergo drug susceptibility testing, especially rapid culture, in order to diagnose DR-TB as soon as possible. However, since HIV patients with pulmonary or extrapulmonary TB are commonly smear negative, DR-TB diagnosis and sensitivity testing can be difficult.

12.4.2 Identification

HIV with TB coinfection should be differentiated from other HIV-related lung diseases including (but not limited to) acute bacterial pneumonia, Kaposi's sarcoma, and *Pneumocystis* pneumonia. Since these diseases have similar clinical manifestations, they should be identified from the typical lesions of the skin and mucous membranes, imaging characteristics, pleural fluid cytology, effectiveness of antibiotic treatment, etc.

12.4.2.1 HIV/AIDS Patients Coinfected with Extrapulmonary TB

HIV/AIDS patients coinfected with lymph node TB should be identified through lymph node biopsy to distinguish from persistent lymphadenopathy, lymphoma, Kaposi's sarcoma, metastatic carcinoma, sarcoidosis, and drug reactions. Patients coinfected with tuberculous effusion should be differentiated from those with effusion caused by cancer, heart failure, renal insufficiency, and liver cirrhosis through conventional biochemical cytological examination of the effusion. HIV/AIDS combined hematogenous disseminated TB should be discerned from bacterial inflammation (including typhoid fever), diffuse type of tumor, atypical mycobacteria, and diffuse infection and connective tissue disease caused by HIV wasting disease syndrome. HIV/AIDS combined tuberculous meningitis ought to be distinguished from cryptococcal meningitis, tumors, bacterial meningitis, and viral meningitis through the examination of cerebrospinal fluid.

12.5 Treatment of TB/HIV

12.5.1 Treatment of HIV/AIDS

Antiretroviral (ARV) drugs block the activity of the enzymes which play important roles in the function and replication of HIV. Highly active antiretroviral therapy (HAART) includes at least three kinds of ARV drugs in combination. Although HAART cannot cure HIV infection, it can significantly inhibit replication of HIV, increasing efficacy and reducing development of drug resistance.

12.5.1.1 Antiretroviral Drugs

Antiretroviral drugs can be divided into protease inhibitors (PIs) and reverse transcriptase inhibitors (RTIs). RTIs include nucleoside analog reverse transcriptase inhibitors (NRTIs), nucleotide analog reverse transcriptase inhibitors (NtRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Common dosage and side effects of the drugs are listed in Table 12.2.

Table 12.2 Common dose and side effects of antiretroviral drugs

Drug	Dose	Side effects
Reverse transcriptase inhibitors (RTIs)		
Nucleoside analog (NRTI)		
Zidovudine (ZDV)	300 mg	Nausea, headache, fatigue, muscle pain, myopathy, anemia, neutropenia
Azidothymidine (AZT)	2 times/day	
Stanvudine (d4T)	40 mg	Peripheral neuropathy, pancreatitis, lactic acidosis
	2 times/day	
	If weight < 60 kg:	
	30 mg	
	2 times/day	
Lamivudine (3TC)	150 mg	Nausea, headache, fatigue, muscle pain, anemia, neutropenia
	2 times/day	
Didanosine (ddI)	400 mg	Nausea, diarrhea, peripheral neuropathy, pancreatitis
	1 time/day	
	If weight < 60 kg:	
	250 mg	
	1 time/day	
Abacavir (ABC)	300 mg	Nausea, fatigue, sleep disorders, allergic reactions
	2 times/day	
Nucleotide analog (NtRTI)		
Tenofovir (TDF)	300 mg	Nausea, diarrhea, fatigue, lactic acidosis, rash
	1 time/day	
Non-nucleoside (NNRTI)		
Efavirenz (EFV)	600 mg	Neuropsychiatric disorders, anxiety, insomnia, rash, liver damage, hyperlipidemia
	1 time/day	
Nevirapine (NVP)	200 mg	Rash, hepatitis
	1 time/day for 14 days, then 200 mg	
	2 times/day	
Protease inhibitors (PI)		
Nelfinavir (NFV)	1250 mg	Diarrhea, nausea, rash
	2 times/day	
Indinavir/ritonavir (IDV/r)	800 mg/100 mg	Nausea, abdominal pain, headache, kidney stones, nausea, diarrhea, fatigue, skin sensitivity, abnormal taste, perioral numbness
	2 times/day	

(continued)

Table 12.2 (continued)

Drug	Dose	Side effects
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg	Abdominal pain, diarrhea, fatigue, headache, nausea, vomiting, pancreatitis
	2 times/day	
	Combined with EFZ or NVP:	
	533 mg/133 mg	
	2 times/day	
Saquinavir/ritonavir (SQV/r)	1000 mg/100 mg	Nausea, diarrhea/nausea, diarrhea, fatigue, skin sensitivity, abnormal taste, perioral numbness
	2 times/day	

Table 12.3 WHO recommended first-line combined ART (Harries et al. 2004)

Regimen	Pregnancy contraindications	Major toxicity
AZT/3TC/EFV or AZT/3TC/NVP	Substitute NVP for EFV in women who are pregnant or cannot tolerate effective contraception	Anemia (AZT), central nervous system symptoms and teratogenicity (EFV), liver toxicity and severe skin rash (NVP)
AZT/3TC/ABC	Limited information on safety (ABC)	Anemia (AZT), ABC hypersensitivity (AZT)
AZT/3TC/PI	Limited information on safety (LPV)	Anemia, diarrhea (NFV), kidney stones (IDV), metabolic side effects (PI)

The standardized and simplified antiretroviral therapy (ART) regimens recommended by WHO advocate combination therapy: two kinds of nucleoside reverse transcriptase inhibitors plus a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor. Common therapies are listed in Table 12.3.

The AIDS Study Group of the Chinese Medical Association (2006) formulated the *AIDS treatment guidelines* and recommends the first-line combination of (AZT or d4T) + 3TC + (EFV or NVP). Alternative therapies are: (AZT or d4T) + 3TC + IDV, ddI + d4T + (EFV or NVP), or AZT + ddI + (EFV or NVP).

12.5.2 Treatment of TB

While the principles, drug selection, and programs of TB treatment for TB/HIV patients are similar to those who are HIV negative, attention must be paid to the interactions between TB and HIV therapeutic drugs. The efficacy of anti-TB treatment is not as good for TB/HIV patients; TB chemotherapy has a 60–70 % cure rate in the TB/HIV coinfected and patients have a high TB recurrence rate. The cure rate in MDR-TB/HIV patients is particularly low: 40–60 % of these patients die during treatment (Wells et al. 2007).

12.5.3 Treatment of TB/HIV

Antiretroviral therapy (ART) can improve the survival rate and reduce the mortality of TB/HIV patients. Anti-TB drugs and ARV drugs can interact with each other and increase liver toxicity. If a patient is not currently on HAART, it is generally recommended that the patient undergo anti-TB treatment before beginning HAART. For patients with advanced AIDS, however, delayed HAART may affect the survival rate. For AIDS patients whose $CD4^+$ T lymphocyte count is <50 cells/mm^3, HAART should be conducted as soon as the anti-TB treatment is effective. For patients whose $CD4^+$ T lymphocyte count is 50–200 cells/mm^3, HAART should begin after the intensive period of anti-TB treatment.

For MDR-TB/HIV patients, there is no current consensus on the best time to start ART after anti-TB treatment. The WHO recommendations are listed in Table 12.4.

If the patients need to take anti-TB drugs and ARV drugs at the same time, the recommended prescription for anti-HIV treatment is AZT/3TC or d4T/3TC together with ABC or an NNRTI. EFZ is the preferred NNTRI because it has lower liver toxicity than NVP; however, the dosage may need to be increased to 800 mg per day. Due to drug interactions, PIs are not recommended while the patient is taking rifampicin.

12.5.3.1 Interactions Between ART and Anti-TB Drugs Affect Drug Selection

Rifampicin can activate the cytochrome P450 (CYP450) hepatic enzyme system, thus increasing the metabolism of PIs and NNRTIs and significantly decreasing their plasma concentration. PI and NNRTI can also enhance or inhibit the function of the CYP450 hepatic enzyme system, which changes rifampicin levels in the blood. This drug interaction between ART and anti-TB therapy will lead to

Table 12.4 ART after TB chemotherapy in MDR-TB/HIV patients (WHO 2008)

$CD4^+$ cell count (cells/mm^3)	ART recommended	When to start ART
CD4 < 200	Yes	2 weeks after the tolerable treatment of MDR-TB
200 < CD4 < 350	Yes	After 8 weeks of MDR-TB treatment[a]
CD4 > 350	Delay[b]	Evaluate the patient monthly to determine ART start time. Check CD4 cell count every 3 months during the treatment of MDR-TB
CD4 cannot be counted	Yes[c]	2–8 weeks after MDR-TB treatment

Note: [a]Clinical evaluation required to start the ART in a timely fashion
[b]If the HIV/AIDS patient develops to stage 3 or 4, start ART
[c]Some patients may start ART too early

ineffective treatment or increased drug toxicity. As rifabutin has a weaker ability to activate the CYP450 hepatic enzyme system, the WHO recommends using rifabutin instead of rifampicin when antivirus and anti-TB treatments are taken concurrently. If rifabutin cannot be used for some reasons, rifapentine can be selected.

Isoniazid and NRTIs (Zidovudine, Zalcitabine, and Stavudine) can cause peripheral neuropathy. Using these two kinds of drugs in combination can increase the incidence of this adverse reaction. In addition, isoniazid can theoretically interact with abacavir; patients taking both medications should be monitored during treatment.

Didanosine, an alkaline drug containing aluminum/magnesium antacid, may reduce the absorption of the fluoroquinolones. Therefore, the combination of these two kinds of drugs should be avoided. If this is not possible, didanosine should be taken 6 h before or 2 h after taking the fluoroquinolone.

Sulfur isonicotinoyl amine B/C is also metabolized by the CYP450 hepatic enzyme system, which suggests they can possibly interact with antiviral drugs. Since the mechanism is not clear, there are no guidelines to adjust the doses of both drugs in combination therapy.

Clarithromycin is a substrate and inhibitor of CYP3A and has a variety of interactions with PIs and NNRTIs. In addition, its efficacy in the treatment of drug-resistant TB is limited, so its use in HIV/TB patients should be avoided.

In areas of high TB/HIV prevalence, the WHO recommends avoiding intramuscular injections of streptomycin and kanamycin and, if possible, using ethambutol (administered orally) instead. This can help reduce infections by syringes and takes in consideration the excessive weight loss of HIV patients in the intramuscular area. In addition, use of ammonia is discouraged because it can cause fatal skin rashes.

12.5.3.2 Application of Glucocorticoids

Glucocorticoids are immunosuppressants which can increase the risk of opportunistic infections for those with HIV. However, when properly administered, glucocorticoids should be given to HIV-infected patients with the following conditions: symptoms of tuberculous meningitis (confusion, neuropathy, or spinal stenosis), tuberculous pericarditis or pericardial constriction, tuberculous pleurisy with severe symptoms and effusion, adrenal insufficiency/adrenal TB, laryngeal TB with fatal airway obstruction, severe allergic reactions, urinary tract TB (to prevent ureteric scarring), or TB infection in multiple lymph nodes which cause compression symptoms.

12.5.3.3 The Treatment of Immune Reconstitution Syndrome

TB/HIV patients may have occasional temporary worsening of TB when starting anti-TB treatment, such as high fever, swollen lymph nodes, increased central nervous system lesions, and worsening chest lesions shown by X-ray. This abnormal

response is considered to be the result of immune reconstitution, as well as the result of giving the antiviral and anti-TB drugs in combination. For severe immune reconstitution syndrome, prednisone can be applied at 1–2 mg/kg for 1–2 weeks, with the dose gradually tapered down.

12.5.3.4 Course of Treatment

There is no current consensus on treatment for TB/HIV patients. Some studies found that HIV-infected TB patients had higher recurrence rates of TB than HIV-negative TB patients, which was related to the short-course chemotherapy. The Chinese Medical Association's *AIDS treatment guidelines* (2006) suggest extending the initial treatment phase of TB therapy to 9–12 months.

12.5.4 Preventive Anti-TB Treatment

Preventative treatment is recommended for those with HIV/AIDS patients who are PPD-positive intravenous drug users, have prior pulmonary TB, have a PPD test induration > 5 mm, and AIDS patients with $CD4^+$ cell counts $<200 \times 10^6$ cells/L^1 (WHO 2008). The *AIDS treatment guidelines* recommend INH continuously for 12 months or taking isoniazid with rifapentine continuously for 4–6 months (AIDS Study Group 2006).

12.6 Adverse Reactions and Monitoring in TB/HIV Combination Therapy

While there are few reports covering the incidence and severity of adverse events in combination antiviral and anti-TB therapy, in general, HIV-infected patients have a higher incidence of adverse drug reactions and this increases as immune function decreases. Common adverse drug reactions of antivirus and anti-TB drugs can be found in Table 12.5.

12.6.1 Treatment of Adverse Reactions

When TB/HIV patients take ART and anti-TB treatment concurrently, care should be taken to avoid drugs with serious adverse reactions and/or overlying toxicity. Adverse drug reactions for TB/HIV patients usually occur 2 months after the start of treatment, depending on the state of their immune systems. For mild adverse

Table 12.5 Potential adverse reactions of anti-TB and antiviral treatment

Adverse reactions	ART drugs	Anti-TB drugs	Notes
Peripheral neuritis	d4T, ddC, ddI	Aminoglycosides Cs, E, Eto/Pto, H, Lzd	Avoid using these drugs in combination. If absolutely necessary, select drugs with low peripheral nerve toxicity
Central nervous system toxicity	EFV	Cs, Eto/Pto, H, Fluoroquinolones	Little data is available on adverse reactions to combined use of Cs and EFV. If prescribing, closely monitor central nervous system toxicity
Depression	EFV	Cs, Eto/Pto, H, Fluoroquinolones	When treated with EFV, 2.4 % of patients have severe symptoms of depression. If depression occurs, consider changing the prescription
Headache	AZT, EFV	Cs	Headache caused by bacterial meningitis, cryptococcal meningitis, or CNS toxoplasmosis should be ruled out. Analgesics (ibuprofen and acetaminophen) can be applied
Nausea, vomiting	d4T, NVP, RTV	E, Eto/Pto, H, PAS, Z	Nausea and vomiting are common adverse reactions; persistent vomiting or abdominal pain may be caused by acidosis and drug-induced hepatitis
Abdominal pain	All ART drugs	Cfz, Eto/Pto, PAS	Abdominal pain is a common adverse reaction, often occurs in the beginning of treatment; however, abdominal pain may be a serious adverse reaction, symptoms of pancreatitis, hepatitis, and early lactic acidosis
Pancreatitis	d4T, ddC, ddI	Lzd	Avoid using these drugs in combination. Gallstones and alcohol are also potential causes of pancreatitis
Diarrhea	ddI, All PIs	Eto/Pto, Fluoroquinolones, PAS	Pay attention to diarrhea caused by opportunistic infections or *Clostridium difficile* infections
Liver toxicity	EFV, NVP, All PIs and RTIs	E, Eto/Pto, Fluoroquinolones,	TMP/SMX can also cause liver toxicity. Viral hepatitis should also be excluded

(continued)

Table 12.5 (continued)

Adverse reactions	ART drugs	Anti-TB drugs	Notes
Rash	ABC, NVP, EFV, d4T, and others	Fluoroquinolones, H, PAS, R, Z, and others	When skin rash appears, avoid using ABC (can cause life-threatening allergic reactions). Avoid using drugs that can cause Stevens-Johnson syndrome
Lactic acidosis	d4T, ddI, AZT, 3TC	Lzd	If a drug can cause lactic acidosis, it should be quickly replaced
Kidney toxicity	TDF (rare)	Aminoglycosides, Cm	TDF can cause kidney damage and, in some cases, acute renal failure. Avoid using injections combined with TDF, as there is little data. Renal function tests recommended once every 1–3 weeks. For patients with renal insufficiency, adjust the dose of ARV and anti-TB drugs
Kidney stones	IDV	None	Ensure adequate water intake to prevent kidney stones. If kidney stones appear, substitute protease inhibitors if possible
Electrolyte imbalance	TDF (rare)	Aminoglycosides, Cm	Diarrhea and/or vomiting can cause electrolyte imbalance. Even without TDF, patients can encounter secondary renal dysfunction and electrolyte imbalance due to the application of injection
Bone marrow suppression	AZT	H, Lzd, R, Rfb	Monitor the blood regularly. If there is bone marrow suppression, AZT and Lzd should be discontinued
Optic neuritis	ddI	E, Eto/Pto (rare)	Abandon drugs that may cause permanent optic neuritis, switch to other drugs without such side effects
High cholesterol	EFV PIs	none	No literature reports that combined treatment can exacerbate high blood cholesterol
Lipodystrophy	NRTIs (especially d4T and ddI)	None	Cause is not known, but changing medications (especially to newer drugs) may help

(continued)

Table 12.5 (continued)

Adverse reactions	ART drugs	Anti-TB drugs	Notes
Glucose dysregulation	PIs	Eto/Pto, Gfx,	Protease inhibitors can cause insulin resistance and hyperglycemia. Eto/Pto makes it more difficult for diabetic patients to control blood sugar with insulin and may lead to low blood sugar and glucose dysregulation. WHO's Green Light Committee no longer recommends gatifloxacin for anti-TB treatment
Hypothyroidism	d4T	Eto/Pto, PAS	Evidence for potential overlying toxicity is inconsistent. Studies have connected clinical hypothyroidism to ART. The combination of d4T, PAS, and Eto/Pto in particular can lead to hypothyroidism

ART drugs: ABC Abacavir, *AZT* Azidothymidine, *d4T* Stanvudine, *ddC* Zalcitabine, *ddI* Didanosine, *EFV* Efavirenz, *IDV* Indinavir, *NFV* Nelfinavir, *NRTIs* Nucleoside analog Reverse Transcriptase Inhibitors, *NVP* Nevirapine, *PI* protease inhibitors, *RTV* Ritonavir, *TDF* Tenofovir
TB drugs. Cfz Clofazimine, *Cm* Capreomycin, *Cs* Cycloserine, *E* Ethambutol, *Eto/Pto* Ethionamide/Prothionamide, *Gfx* Gatifloxacin, *H* Isoniazid, *Lzd* Linezolid, *PAS* para-aminosalicylic acid, *R* Rifampicin, *Rfb* Rifabutin, *Z* Pyrazinamide
Others: CNS Central Nervous System, *TMP/SMX* Trimethoprim/sulfamethoxazole

reactions during treatment, it's not necessary to stop the drug. For severe adverse reactions (such as skin rashes, deafness, jaundice, allergy, and alanine transaminase >200 IU), the doctor must discontinue the drug immediately and actively address the adverse reactions.

12.6.2 Monitoring the Combination Therapy

During combination therapy, patients should be monitored for medication safety and efficacy through clinical assessment and laboratory tests.

Safety monitoring involves testing blood, urine, liver function, kidney function, electrolytes, glucose, lipids, and thyroid function on a regular basis (every 2–4 weeks) according to the treatment, as well as testing for adverse reactions as early as possible.

Efficacy monitoring involves sputum culture, sensitivity testing, chest X-ray or CT scan, $CD4^+$ T lymphocyte count, and other laboratory examinations regularly according to the relevant guidelines. If the treatment is effective, the patient's clini-

cal signs and symptoms can improve, including negative sputum results, weight gain, $CD4^+$ lymphocyte count increasing 30 % after 3 months of treatment and/or increasing 100 cells/mm^3 after 1-year treatment, decrease of plasma HIV RNA levels, and decrease of incidence and severity of HIV-related disease. If the anti-TB treatment or ART fail, doctors should adjust the therapy accordingly.

12.7 Collaborative TB/HIV Treatment

In 2004, the WHO developed a TB/HIV collaborative strategy to control TB/HIV and reduce its burden (Harries et al. 2004). WHO recommends the establishment of resources, health care workers, and facilities to counteract the impact of TB/HIV. HIV/AIDS health care institutions should implement TB infection control measures. In TB/HIV high-risk areas or institutions, medical teams should conduct sputum tests (smear or culture) for suspected TB patients and provide HIV testing and counseling. Pulmonary and extrapulmonary TB should be diagnosed using standard and new methods, including mycobacterial sputum culture and other rapid diagnostics. For active TB/HIV coinfection, the patient should be given sulfamethoxazole prophylactic therapy and monitored for signs of its toxicity. Patients should be given additional nutrition and socioeconomic support, and follow-up treatment should be arranged for all patients.

Drug-resistant TB is a special concern in the HIV positive. Drug susceptibility testing and/or rapid drug resistance detection should be performed at the start of anti-TB treatment for all of HIV-infected patients with active TB. ART should be quickly initiated for DR-TB/HIV patients, with care to monitor and prevent immune reconstitution syndrome. When testing is not available, empirical treatment with second-line anti-TB drugs should be considered for patients with a high suspicion of having DR-TB/HIV. Additionally, surveillance and surveys are needed to monitor epidemiological trends in DR-TB/HIV.

Communication and effective collaboration between existing TB and HIV/AIDS programs is critical for TB/HIV coinfection control. A coordinated framework benefits both TB and HIV programs from the integrated care of coinfected patients to the implementation of complementary prevention and intervention measures.

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Chapter 13
Concurrence of Tuberculosis and Other Major Diseases

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13.1 Concurrence of Tuberculosis and Diabetes

In medical literature, descriptions of concurrence of tuberculosis (TB) with diabetes mellitus can be traced back to Richard Morton's 1694 text, *Phthisiologia*, which suggested that the association between the two diseases could have been observed as early as in Roman times. Nowadays, continuous development of the social economy, which has dramatically changed people's daily diets, has been sharply increasing the incidence of diabetes worldwide (Ottmani et al. 2010). At the same time, the TB epidemic has experienced a resurgence, especially in developing countries in the past two decades, thus resulting in the increased incidence of the combination of these two diseases (Hassani et al. 2005). The two diseases interact to cause additional clinical problems, and this has become a new challenge in TB control (Dooley and Chaisson 2009).

Diabetes is a major risk factor for people infected with TB to develop active disease. Several case–control studies have shown that the relative odds of developing TB in diabetic patients ranges from 2.44 to 8.33 compared with nondiabetic patients (Mboussa et al. 2003; Coker et al. 2006; Jabbar et al. 2006; Shetty et al. 2006). Diabetes is also the most common clinical complication in TB patients. TB patients with diabetes usually have more risk factors for treatment failure, including a higher proportion of smear-positives and large numbers of voids. Patients with concurrence of TB and diabetes also increase the spread of TB infection, thus aggravating the TB epidemic.

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13.1.1 Pathogenesis of TB/Diabetes

Chronic diabetic patients almost always develop clinical symptoms in cardiovascular, nervous, urinary, and immune systems, eventually resulting in dysfunctions of immune system and metabolic disorders. Many studies have shown that abnormalities of some critical cytokine secretions, including IL-1β, TNF-α, and IFN-γ, might be responsible for nonspecific immune deficiency in diabetes patients (Banerjee and Banerjee 2005; Stalenhoef et al. 2008; Al-Attiyah and Mustafa 2009). The onset of TB disease and worsening of TB infections are related to immune deficiency or dysfunction (Stalenhoef et al. 2008).

Diabetes patients' long-term exposure to high blood sugar can also affect their white blood cells' ability for phagocytosis and exocytosis. Electronic microscopy (EM) studies show that white blood cells of diabetics exhibit less protrusion and deformation, reduced phagocytosis and lysosomal functions, and that cytoplasmic organelles are rarely seen. The lower functional ability of alveolar macrophages in diabetics provides more favorable conditions for the replication of TB pathogen, thus increasing TB susceptibility in diabetic patients. In the bronchoalveolar lavage fluid of TB patients with diabetes, alveolar macrophages and their H_2O_2 production are both significantly lower than normal. These factors are negatively correlated to the range of lung lesions and the bacteria quantity in sputum.

Fat metabolism disorders in diabetic patients are often accompanied by hyperlipidemia, which means their levels of triglycerides are higher than normal. One of the triglyceride metabolic products, glycerol, is an important carbon source for *Mycobacterium tuberculosis* growth and reproduction. Deficient protein metabolism may lead to hypoproteinemia and malnutrition which reduces the body's defense capabilities and repair ability.

Many diabetic patients also experience liver dysfunction, reducing the conversion of carotene to vitamin A. As a result, the airway epithelial cells decline in defense. The thickened alveolar epithelium could decrease diffusion capacity and increase glycated hemoglobin, which is not conducive to oxygen release. Tissue with lower oxygen content increases the incidence of TB.

TB has an adverse impact on diabetics as well. Tuberculous fever will increase insulin consumption and the burden on islet cells (Xie 1999). At the same time, chronic consumption of active TB could lead to islet cell malnutrition and decreased function (Dooley and Chaisson 2009). As a result, the risk of people developing diabetes increases, or existing diabetes can be aggravated, and some acute complications such as diabetic ketoacidosis may be induced.

13.1.2 Diagnosis of TB/Diabetes

Patients with both diabetes and pulmonary TB almost always have diabetes first (Feleke et al. 1999). The incidence of TB is higher in diabetic than nondiabetic patients, with the main onset age of 40–69 years (Restrepo et al. 2007). Diabetic

patients may be asymptomatic in the early stage, but once high blood sugar occurs, polydipsia, polyphagia, polyuria, weight loss, and other symptoms will appear, and even diabetic ketoacidosis will occur in severe patients. The WHO officially announced the diabetes diagnostic criteria in 1999: Fasting Plasma Glucose (FPG) level ≥7.0 mmol/L (126 mg/dL); Oral Glucose Tolerance Test (OGTT) glucose levels ≥11.1 mmol/L (200 mg/dL) at the 2 h time point; patient has symptoms of high blood sugar, and his/her plasma glucose is ≥11.1 mmol/L (200 mg/dL) at any time. If there are no symptoms of high blood sugar, then one of these criteria (FPG, OGTT, or non-fasting plasma glucose levels) should be checked again. In 2010, the American Diabetes Association added a glycosylated hemoglobin (HBGA1c) value of ≥6.5 % to the diagnostic criteria above (American Diabetes Association 2010).

Patients with both diabetes and pulmonary TB do not have specific respiratory symptoms. They may have symptoms of TB such as cough, sputum, fever, night sweats, and so on, but the symptoms are often more acute onset, with purulent sputum and hemoptysis. Therefore patients with both diabetes and pulmonary TB are easily misdiagnosed as having acute pneumonia or pulmonary suppuration. Lung wet rale occurs if there are extensive lesions or combined infections. Often, chest X-rays show that saturated, exudated, or cheese-like lesions are most common and they are easily fused, forming cavities and spreading in the bronchus. The lesion sites are not only at the common preferred site of TB but all over the lung lobes as well. The rate of lower lung lobe lesions of TB is higher in TB/diabetic patients than the patients who have TB alone. Cavity formation is more common in TB/diabetic patients, and fluid levels can occur within the hollow region (Pérez-Guzmán et al. 2000, 2001). In addition, the rate of lower lung lobe lesions of TB and cavity formation will increase as the years progress. The sputum smear-positive ratio is higher in TB/diabetic patients than those without diabetes mellitus and there are more drug-resistant (DR) and multidrug-resistant (MDR) patients in the former group (Bashar et al. 2001; Subhash et al. 2003).

In patients with diabetes mellitus, it is important to distinguish between those infected with TB and those with other pulmonary infectious diseases. Diabetics are 32.7–90.5 % more susceptible than the general population to infection with respiratory diseases like pneumonia and acute exacerbation of chronic bronchitis (Marvisi et al. 1996). Characteristics such as cough, sputum, and fever should be noted in the diagnosis. Blood and sputum pathogens should be tested. When performing imaging examination, samples should be taken of tumors/lesions to distinguish between TB and lung or bronchial cancer.

13.1.3 Treatment of TB/Diabetic Patients

For the anti-TB treatment of patients with TB/diabetes, three or four drugs, such as isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), ethambutol (EMB), and/or streptomycin (SM), are usually applied together in the chemotherapy program. Generally speaking, it takes 1–1.5 years to complete a whole course of treatment for

TB, which is longer than for patients with pulmonary TB alone. If drug-resistant TB is confirmed, an even longer course is required with the appropriate drugs according to drug susceptibility testing. Some scholars believe that short-course chemotherapy programs are also appropriate for concurrent treatment of these two diseases. Studies have shown that the sputum conversion rate of new smear-positive patients after 6 months treatment could reach 94 %. Sputum conversion can fail when the patient is older than 45, has a high pretreatment smear grade, and/or has lung field lesions in more than two lung lobes (Banu Rekha et al. 2007). At present, there has not been a randomized controlled study of multicentered large numbers of samples, and there is no standard program indicating the specific time for the course of treatment. It is thought that blood glucose control is the key point for treatment in the patients with both TB and diabetes. If patients' blood glucose control is good to excellent, their sputum conversion rate after both 2 months and after 6 months of treatment will be higher than those whose blood glucose is poorly controlled (Zeng et al. 2006). But there are different views (Balasubramanian et al. 2007). The recurrence rate of pulmonary TB combined with diabetes is higher than that of nondiabetics, especially for the patients with poor glucose control.

Treatment of diabetes is a comprehensive program involving health education, diet, exercise, medication, and blood glucose monitoring. It aims to maintain blood sugar within a standard safety range and to avoid or reduce the incidence of complications. Specific measures could refer to the diabetes-related treatment guidelines. The TB patients' physical status is in chronic consumption, so they require a reasonable calorie intake. High-quality protein should be the main source, which, along with increased intake of both vitamins and dietary fiber, could improve in TB site repairing. Patients with hypoalbuminemia should take special care to increase their protein intake. In addition to the daily calories required (calculated according to patient body weight and activity), appropriate additional energy could be added by increasing carbohydrates to up to 45–60 % of the total calories consumed (Chinese Diabetes Society, China Medicine Doctor Association Nutrition Doctor Specialized Committee 2015). Some studies have shown that the plasma concentration of anti-TB drugs in TB patients with diabetes may be reduced, thus reducing the effectiveness of TB treatment (Nijland et al. 2006; Ruslami et al. 2010). Anti-TB drugs can impact diabetes. INH can interfere with the normal glucose metabolism, increasing sugar in urine and blood and increasing peripheral neuritis as well. RIF is a liver enzyme inducer, which could accelerate the metabolism of sulfonylurea and shorten its half-life, weakening its hypoglycemic effect. Aminoglycosides and fluoroquinolones are harmful to the kidneys. Ethambutol can cause optic neuritis. These drugs should be used with caution in the clinic and patients should be monitored.

As the incidence of diabetes increases worldwide, it becomes increasingly important to control and treat TB effectively in diabetic patients. More prospective studies should be carried out for further improvement to achieve the aim of early detection and early treatment, especially in developing countries.

13.2 Silicosis and TB

Silicosis is due to the long-term inhalation of dust containing free silica, with extensive nodular fibrosis in lung tissues as its main characteristic (Barboza et al. 2008). There are three clinical forms: chronic silicosis, acute silicosis, and accelerating silicosis between the chronic and acute forms. Different clinical manifestations have significant relationships with the exposure of dust concentration levels, silica content, and exposure times. Chronic silicosis is the most common clinical form.

Silicosis and TB are correlated. Studies have shown that pulmonary TB incidence for silicosis patients is 2.8–39 times greater than in the normal population and the incidence of nonpulmonary TB is 3.7 times greater (Barboza et al. 2008). About 61 % of silicosis patients also have pleurisy.

13.2.1 Pathogenesis of Concurrence of Silicosis and TB

We don't know exactly why patients with silicosis can easily suffer TB. TB progression is correlated with macrophages (the effector cells) and T cells (the reactive cells) of the cellular immune system. Silica dust has a cytotoxic effect on lung macrophages, causing metabolic damage to pulmonary macrophages and leading to macrophage necrosis. It was recently found that there is surfactant-associated protein A (SP-A) in silicosis bronchial washing fluid (Lesur et al. 1993). SP-A can activate alveolar macrophages and inhibit the formation of free nitrogen, making patients susceptible to *M. tuberculosis* (Samten et al. 2008). In addition, *M. tuberculosis* may escape from macrophage phagocytosis by going into the silica nodules. Activated macrophages can swallow silica very quickly and then the cell's own lysosomes release and collapse. The cell dies quickly, releasing many materials that could stimulate fibroblasts. As a result, pulmonary capillary beds and the lymphatic system can be seriously damaged, with blood vessel walls thickened and deformed. The lumen can narrow or become occluded, reducing blood circulation to the lungs. The reduced blood supply weakens the lung tissue's resistance to TB bacteria. Pulmonary lymphatic system fibrosis can prevent the lymphatic system from resisting *M. tuberculosis* invasion.

While the pathogenesis of silicon TB is the result of many factors, silica dust deposited in the lung can destroy the cellular immune response to TB. This makes acquired immunity to TB hard to establish in silicosis patients.

13.2.2 Diagnosis and Identification of Silicon TB

Diagnosis of silicon TB includes diagnosis of each disease. The first step is to make a definite diagnosis of silicosis, and then to test whether it is combined with TB. If somebody has close contact with silica dust, clinical manifestation and imaging

features should be analyzed to make a comprehensive diagnosis of silicosis. Sputum smear or bacteria culture is the most reliable method in diagnosis of silicon TB. Generally speaking, the sputum bacteria positive rate of patients with silicon TB is higher due to high cavity incidence. But there are concerns that it is easy to get false negative results for silicosis because of extensive fibrosis and bronchial distortion which complicate the discharge of *M. tuberculosis* (Xie 1999; Chen et al. 2005). Therefore, the bronchial alveolar fluid (BALF) smear or *M. tuberculosis* culture and/or bronchial biopsy can be used for diagnosis if necessary.

Silicosis patients may have TB if their chest X-ray shows the following signs as noted by Calvert et al. (2003):

- There are small pieces of asymmetrical shadows with uneven density in the apex of the lung or sulcus of the subclavian artery.
- The silicon nodules in the upper and middle lung lobes increase significantly in a short period of time, and the nodules' profiles are not discernable, with various ranges in size and density.
- There are sheets of asymmetrical shadows with indistinct profile and uneven density which are connected to lung hila by cable-like shadow of draining bronchus.
- The shadow bulk significantly increases within a short period of time, with no draw back towards the heart, and the lesions spread mainly anterior or around, instead of in a vertical direction into the ribs.
- Big and irregular cavities form in a short period, and lesions disseminate ipsilaterally or contralaterally.
- There are lumpy shadows with unclear outlines, and extensive pleura that are thickened and adhering locally.
- There is pleural effusion (fluid leakage excluded).
- After regular anti-TB treatment for more than 6 months, the abnormal lung shadows are significantly improved.

Silicon TB should be distinguished from other lung diseases because its various X-ray patterns are similar to the imaging of other lung diseases. Silicosis nodes should be distinguished from lung cancer and metastatic lung cancer. Lumpy silicon TB should be distinguished from lung cancer. Lumpy silicon TB should be identified from pure bulk lesions. Distinction should be made between silicosis TB cavity and pure silicosis cavity or pure TB cavity. Silicon TB should be identified with the early phase of silicosis. Identification should be made to distinguish silicon TB from pneumonia (Ehrlich et al. 2006).

13.2.3 Treatment of Silicon TB

Treatment for silicon TB includes two parts: silicosis treatment and TB treatment. Treatment principle for silicosis is to take comprehensive measures and control complications. Its aim is to delay the progression of silicosis, reduce patient suffering, and to prolong and improve the quality of life. There is no effective drug for

silicosis, and the progression of TB is faster than that of silicosis. Active TB can even promote the worsening of silicosis if it is not under control. Therefore, the main program for silicon TB treatment is the same as standard TB control treatment: a three- or four anti-TB drug chemotherapy program is adopted, including INH, RIF, PZA, EMB, SM, and so on, with a 3-month initial phase followed by a 6-month continuation phase (3HRZE(S)/6HR). In cases of MDR-TB, an individualized program of chemotherapy combined with silicosis treatment should be mapped out based on the patient's medication history and TB drug sensitivity results. About 4–5 drugs can be used together with at least 2–3 kinds of sensitive drugs, with the whole course of treatment lasting 18–24 months. The program performs well in the local clinic. Because the treatment course for silicon TB is long, and many types of medication are used, extra attention should be paid to drug toxicity.

13.3 Combined Pulmonary Infection

TB is a chronic lung infection. Clinically, treatment of patients with TB in combination with other infections is straightforward. The clinical characteristics of patients with severe pulmonary TB are a long duration of treatment and repeated deterioration, resulting in bronchial pulmonary structural damage. Lung disease is extensive and always accompanied with cavity, bronchial lesions (bronchial mucosal edema, granulation tissue, and scar stenosis), pulmonary atelectasis, bronchiectasis, and pleural thickening which can induce secondary pulmonary infections. In addition, when diagnosed with other risk factors, the onset age of TB is older. Because of upper respiratory mucous membrane and cellular immune function decline, impaired swallowing reflex can easily lead to the inhalation of pathogens and dysfunctional airway clearance. The elderly can experience serious dysfunction of pulmonary ventilation and/or pulmonary air exchange, which could induce respiratory failure, even leading to death once they get pulmonary infection.

13.3.1 Clinical Types of Combined Pulmonary Infection and Pathogen Distributions

There are different types of TB-related lung infection classifications according to the different pathogens and clinical characteristics involved (Ma et al. 2006).

13.3.1.1 Lung Structural Damage

Lung structural damage caused by TB can include bronchiectasis, pulmonary cavities, and other injury that can leave patients vulnerable to secondary pulmonary infection. Complications include empyema, bronchial fistula, and secondary bacterial infections. Infection of gram-negative bacteria, especially *Pseudomonas*

aeruginosa, Aspergillus, and anaerobic bacteria, is significantly increased. In addition, the number of nontuberculous mycobacterial infections combined with pulmonary TB is increasing (Ma and Wang 2010). The infections above are community-acquired but differ from the general community-acquired pneumonia (CAP) because of the underlying damage to the lung structure.

13.3.1.2 Hospital-Acquired Pneumonia (HAP)

HAP in TB inpatients can be caused by special circumstances in the hospital or by iatrogenic factors. TB patients (especially the ones with severe pulmonary TB) are prone to get HAP due to their prolonged hospitalization, time in the ICU because of respiratory failure, or receiving mechanical ventilation. The incidence of hospital-acquired infections in pulmonary TB patients is higher than that in non-TB patients (Chen et al. 2011). The main infection area is the lung, and the main pathogens are gram-negative bacteria, especially Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia*, *Proteus*, etc.) and G-glucose non-fermenting bacteria (*P. aeruginosa* and other *Pseudomonas*, *Alcaligenes*, *Xanthomonas maltophilia*, and *Acinetobacter* such as nitrate-negative bacilli and *Acinetobacter baumannii*). Such bacteria have high drug resistance and ineffective anti-infective treatment; infection results in high mortality. The detection rate of *Candida* spp. is also high, but the clinical significance of this is controversial (Chen et al. 2012).

13.3.1.3 Immunosuppression

Immunosuppression can lead to the compound infection of TB mixed with other pathogens such as gram-positive cocci, gram-negative bacteria, anaerobic bacteria, fungi, viruses, *Pneumocystis carinii*, and so on.

13.3.1.4 Aspiration pneumonia (AP)

AP refers to a pulmonary syndrome caused by the secretions of mouth, throat, and stomach flowing into the throat and lower respiratory tract. If a small amount of secretions is inhaled, it can lead to bacterial aspirated pneumonia. With a large amount, acute chemical aspirated pneumonia can develop. Aspiration pneumonia is the major risk factor leading to death for elderly people suffering from neurological or cerebrovascular disease. Radionuclide tracer scans demonstrated that about 70 % of the community-acquired pneumonia in the elderly is caused by silent aspirations (Kikuchi et al. 1994). Pathogens of different patients can vary: gram-negative bacilli (including *Haemophilus influenzae*, *P. aeruginosa*, *K. pneumoniae*, *Stenotrophomonas maltophilia*, and *E. coli*) and *Staphylococcus aureus* are common in continuing care facility-acquired aspiration pneumonia (CCFAP) and hospital-acquired aspiration

pneumonia (HAAP) patients. For community-acquired aspiration pneumonia (CAAP) patients, *Streptococcus pneumoniae* can also be isolated from their sputum. In addition, anaerobic bacteria (mainly including *Bacteroides*, *Peptostreptococcus*, and *Fusobacterium*) are also an important kind of pathogen for AP.

13.3.1.5 Pulmonary TB Combined with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

The main symptom of COPD is aggravated shortness of breath, which is always accompanied with wheezing, chest choking, aggravated cough, increased sputum production, increased sputum purulence and/or viscosity changes in sputum, and fever. In addition, symptoms such as whole body malaise, insomnia, drowsiness, fatigue, depression, and mental disorders could also appear. There are many factors that cause AECOPD, 40–60 % of which are due to bacteria (*H. influenzae*, *S. pneumoniae*, *Moraxella catarrhalis*, *P. aeruginosa*, and other gram-positive or gram-negative bacteria), about 30 % due to viruses (influenza, parainfluenza, rhinovirus, coronavirus, adenovirus, and respiratory syncytial virus), and 5–10 % due to atypical pathogens (rare *Chlamydophila pneumoniae* or *Mycoplasma pneumoniae*, but not *Legionella*).

13.3.2 Diagnosis of TB-Combined Pulmonary Infection

Diagnosis of pulmonary infection usually depends on the comprehensive analysis of clinical symptoms, signs, peripheral blood, imaging data, pathogenic microbiology, and serology.

13.3.2.1 Confirmation of TB-Combined Pulmonary Infection

As a special kind of infection, TB is just the same as other pathogen infections in symptoms, signs, peripheral blood, and imaging. Due to interference by mouth and throat bacteria and other factors, the pathogens of the respiratory tract that are detected positive cannot be identified as the real pathogens that infect the lower respiratory tract. Therefore, the diagnosis of TB combined with pulmonary infection is difficult, and the following aspects should be heeded in clinical practice:

1. When symptoms such as cough, increased sputum, purulent sputum, and fever appear, the worsening of TB or hidden lesions of TB must first be excluded.
2. The clinical manifestations in elderly patients with pulmonary infection are often atypical; dyspnea and tachycardia may be the first symptoms indicating a combined infection. Imaging is an effective tool for this diagnosis. Imaging characteristic is valuable in diagnosis of pulmonary TB combined with mycetoma.

3. The following imaging features often suggest additional pulmonary infection in TB patients:
   - The level of emerging liquid from the TB cavity is higher than before, and the infiltrating lesion tends to absorb or the proliferative change around the cavity wall increases.
   - Emerging abscess or cavity lesions.
   - Substantial lesions appear besides the former lesion, or there is infiltrated shadow that does not fit the characteristics of spreading along the bronchial tubes.

   Conditions such as hemoptysis causing blood or blood clots gathering in or blocking the bronchial alveoli, or TB in combination with acute respiratory distress syndrome (ARDS) or pulmonary edema or atelectasis, should be identified.
4. Serological tests are helpful in diagnosis. Antigen and serological examination is mainly used for the diagnosis of atypical pathogens, including *Legionella*, mycoplasma, chlamydia, and viruses. A procalcitonin (PCT) test can help to distinguish bacterial infection. A (1–3)-β-D-glucan Assay (beta-glucan test) can help to diagnose a variety of invasive fungal infections except cryptococcosis or infections caused by zygomycetes such as mucormycosis, phycomycosis, and basidiobolomycosis. Detection of Galactomannan (GM) in the blood contributes to the diagnosis of aspergillosis.

13.3.2.2 Etiological Diagnosis

Etiological diagnosis is very important in guiding the correct and effective antibiotic in the clinic. Before the pathogen is confirmed, some clinical characteristics and imaging figures are helpful to deduce what the pathogen is and offer a guide for treatment.

Sputum

Bacterial pneumonia is often characterized by large amounts of yellow sticky sputum. Sputum from *K. pneumoniae* infection is brick red, jelly-like, and very sticky, similar to strawberry jam. *S. pneumoniae* infection is characterized by rust-like sputum. Sputum of *P. aeruginosa* pneumonia is green. There is a characteristic smell to anaerobic bacteria infecting sputum. Sputum of pulmonary amoebic infection is brown with a stench. *Candida albicans* infection has white and transparent sputum, which is very sticky, hard to cough, and could be pulled into a wire shape (Xu 2005; Johnson et al. 2008).

Imaging

Images of *S. pneumonia* infection have a uniform density distribution in the lobe, segment, or sub-lung segment, but the pulmonary TB patient who is coinfected with other pathogens often has slice or dot-like shadows. *S. aureus* infection shows multiple pulmonary infiltrates or lobar segment inflammatory changes. It begins as flocculent shadows, then its density increases, appearing as translucent honeycomb areas or cavities. Then, one or more pneumatoceles appear around the shadow of the inflammation area which could increase or disappear rapidly in a short time, accompanied by pleural effusion or pneumothorax. For the blood-borne infected patient, mass slice or bulk-like shadow is distributed at both sides, and cavities are easily formed. Early infection of *K. pneumoniae* appears lobularly invasive, then rapidly expands to large-lobe consolidation, with irregular translucent areas. Curved bulging often appears in the fissure of the lobe (lobe bulging sign) because of its thick and heavy exudate. In *H. influenzae* infected cases, 75 % showed changes characteristic of bronchial pneumonia, and the other 25 % appeared lobular or with segmented opaque shadows. The *P. aeruginosa* infected lung has widespread nodular and patchy shadows, mainly in the lower lung, and there are multiple small abscesses, which can merge together with each other to form a large, consolidated shadow. *M. pneumoniae* infection can be found in diverse forms, with a vague, feathery, or uniform shadow. In general, a shadow close to the lung hila is thick, gradually fading along the lung lobes with an obscure edge. The lesions are movable, but a few shadows are patchy and slice-liked. Rickettsial infection has a patchy shadow or an emerging consolidating shadow with uneven density. Its distribution is segmental or lobular, associated with a small amount of pleural effusion. A feature of pulmonary aspergillosis is that aspergillomata can move with a change in body position when performing the chest imaging test.

Etiology Examination

Pathogens that cause lung infection include bacteria, fungi, viruses, and protozoa. The common inspection methods include smear observation through light microscopy, culture identification, histopathology, immunology, and molecular biology techniques. The following points should be attended to in respiratory specimen collection:

1. The specimen should be treated quickly. For example, the rate of isolating *S. pneumoniae*, *S. aureus*, and some gram-negative bacteria will be reduced if the specimen is stored at room temperature for 2–5 h.
2. The role of smear examination cannot be ignored. Smears of some pathogen-caused infections (such as from *S. pneumoniae*, *H. influenzae*, acid-fast bacilli, *Nocardia* and other actinomycetes, *Candida*, *Cryptococcus*, *Aspergillus*, *Mucor*, and *P. carinii*) can provide information for a clear and probable diagnosis or even a definitive one.

3. Sampling should be from the bronchus fiber mirror brush or bronchoalveolar lavage fluid (BALF) in order to reduce contamination from normal flora of the upper respiratory tract.
4. Quantitative culture results are important. If the concentration of bacteria or fungi in quantitative cultures of sputum is $\geq 10^7$ cfu/mL, the pathogen can be considered a lung infection pathogen; if the concentration is $\leq 10^4$ cfu/mL, it should be regarded as contamination. If the concentration is between the above two, reculturing and retesting is recommended. If the concentration is between 10^5 and 10^6 cfu/mL, and the retest shows the same result, the bacteria can be considered an infecting pathogen. If the sample is from bronchoscopy or an artificial airway, a concentration of $\geq 10^5$ cfu/mL indicates an infecting pathogen. If the specimen is from the BALF, a concentration of $\geq 10^4$ cfu/mL indicates an infecting pathogen. If the sample is from a brush used to prevent contamination, or from BALF that employed contamination prevention measures, a quantitative concentration $\geq 10^3$ cfu/mL indicates an infecting pathogen (Woodhead et al. 2011).

13.3.2.3 Evaluation of the Clinical Significance of Pathogen Positive Results

There are many methods that can detect pathogen-induced lung infections, but the positive result should be considered strongly when judging because of the limitations of existing technology and normal flora contamination. The following criteria refer to the standards of the Chinese Society of Respiratory Diseases as noted by the Chinese Thoracic Society (2006).

Confirmation of Pathogen Diagnosis

1. Pathogen has been detected from blood or pleural fluid culture.
2. The pathogen concentration cultured from bronchoscopy or artificial airway specimens is $\geq 10^5$ cfu/mL, or $\geq 10^4$ cfu/mL in BALF samples, or $\geq 10^3$ cfu/mL in BALF specimens collected using contamination prevention measures.
3. Cultured results respiratory tract specimens are positive for *M. pneumoniae*, *C. pneumoniae,* or *Legionella pneumophila*.
4. Serum antibody titers of serum *M. pneumoniae*, *C. pneumoniae*, or *L. pneumophila* change (increase or decrease) four or more times; at the same time, *M. pneumoniae* antibody titers (complement fixation test result) are ≥1:64, pneumonia antibody titers (micro-immunofluorescence test) are ≥l:32, or *L. pneumophila* antibody titers (indirect fluorescent antibody method) are ≥1:128.
5. Urinary antigen test of *L. pneumophila* (enzyme-linked immunosorbent assay) is positive.
6. Antibody titers to serum influenza virus or respiratory syncytial virus change (increase or decrease) four or more times over multiple samples.
7. A urinary antigen test is positive for *S. pneumoniae* (via immunochromatography, except in children).

Prompt Etiological Diagnosis

1. The dominant bacteria cultured from qualified sputum specimen with slow growth ($\geq 10^6$ cfu/mL).
2. There is a small amount of bacteria growing in the sputum specimen, and it is consistent with the smear microscopy examination result (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*).
3. The same bacteria are cultured repeatedly in separate samples within 3 days.
4. The serum *C. pneumoniae* IgG antibody titer is ≥1:512 or the IgM antibody titer is ≥1:16 (micro-immunofluorescence test).
5. The serum *L. pneumophila* antibody titer is ≥1:320 (tube agglutination test) or the IgG antibody titer is ≥1:1024 (indirect fluorescent antibody test).

Diagnosis of Unknown Pathogen

There are a variety of pathogenic bacteria which grow poorly ($<10^6$ cfu/mL) in sputum culture medium. The sputum specimen may be culture positive for normal colonized bacteria of upper respiratory tract (such as *Streptococcus viridans*, *Staphylococcus epidermidis*, nonpathogenic *Neisseria*, and *Corynebacterium diphtheria*). If none of the diagnostic criteria of "Confirmation of Pathogen Diagnosis" section above are met, then a diagnosis of an unknown pathogen may be considered.

13.3.3 Choice of Antibiotic(s) for Treatment of Lung Infection

The choice of treatment is dependent on the nature and severity of the infection.

13.3.3.1 Community-Acquired Pneumonia (CAP)

The choice of antibiotics for TB patients coinfected with CAP is the same as those for CAP patients without TB as long as there is no bronchial pulmonary structural damage. In patients with bronchial pulmonary structural damage or who are undergoing anti-TB treatment, attention should be paid to gram-negative bacterial infections. Antibiotic treatment should begin as soon as possible, as delay in treatment can have severe consequences and prognosis is closely related to the time when treatment is initiated. Taking the first dose of antibiotics within 4 h after the disease onset is optimal. For life-threatening severe pneumonia, it is suggested to use a broad-spectrum antibiotic in the early stage, and pertinent or de-escalation therapy can be applied according to the pathogen examination when the patient is in stable condition. Antibiotic treatments for mild and severe coinfections as recommended by the Chinese Thoracic Society (2006) are detailed below. Note that empirical antiviral treatments are not recommended for patients who are suspected of

influenza virus infection. Combined antiviral therapy is only used for high-risk patients who have typical flu-like symptoms (fever, myalgia, malaise, and respiratory symptoms) with less than 2 days onset and may also be used preventatively in the influenza epidemic period.

TB Patients Coinfected with Mild Pulmonary Infections

For TB patients coinfected with mild pulmonary infections, common pathogens are *S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, and *C. pneumoniae*. Suggested antibiotics for treatment include penicillins (penicillin, amoxicillin, etc.), macrolides, doxycycline, and the first or the second generation of cephalosporins.

TB Patients Coinfected with Severe Pulmonary Infections

A diagnosis of severe pneumonia can be given if there are one or more of the following:

- Disturbance of consciousness
- Respiratory rate $\geq$ 30 times/min
- Partial pressure of arterial oxygen (PaO_2) <60 mmHg; partial pressure arterial oxygen and fraction of inspired oxygen ratio (PaO_2/FiO_2) <300; mechanical ventilation treatment is required
- Systolic blood pressure < 90 mmHg
- Concurrent septic shock
- X-ray showing bilateral or multi-lobe involvement, or lesions expanding $\geq$50 % within 48 h of hospitalization
- Oliguria: urine output < 20 mL/h or combined acute renal exhaustion that requires dialysis treatment

Patient treatment depends on the risk factors for infection by *P. aeruginosa*. The risk factors for *P. aeruginosa* infection include:

- Structural lung disease (such as bronchiectasis, pulmonary cysts, and diffuse bronchiolitis)
- Use of glucocorticoids (prednisone > 10 mg/day)
- Over the past 1 month, broad-spectrum antibiotics are used more than 7 days
- Malnutrition
- The number of neutrophils in peripheral blood is less than $1 \times 10^9\ L^{-1}$

If none of these risk factors are present, the main pathogens are *S. pneumoniae*, aerobic gram-negative bacteria, *L. pneumophila*, *M. pneumoniae*, *H. influenzae*, and *S. aureus*. Antimicrobial drug combinations include the third generation of cephalosporins combined with macrolides, β-lactam/β-lactamase inhibitors (such as amoxicillin/clavulanic acid or ampicillin/sulbactam) combined with macrocyclic lactones, and carbapenems combined with macrolides.

If there are risk factors for *P. aeruginosa* infection, the main pathogens are those listed previously plus *P. aeruginosa*. Antimicrobial drugs include β-lactam/β--lactamase inhibitor which have anti-*Pseudomonas* activity, carbapenems, β-lactam antibiotics combined with macrolides (with an aminoglycoside if necessary), and β-lactam antibiotics which have anti-Pseudomonas activity combined with intravenous injection of fluoroquinolones.

Course of Antibiotic Treatment

It is suggested that antibiotic treatment should last at least 5 days and the patient's normal body temperature should be maintained for 48–72 h. There should not be more than one kind of CAP-related clinical condition by the end of the treatment. If the initial treatment is not effective or there is concurrent outer-pulmonary infection, the treatment time should be prolonged. Treatment courses are different due to differences in pathogens and their high degree of variety. The complete absorption of the shadow of the lung cannot be considered as the standard for cessation of antibiotics. For ordinary bacterial infections such as *S. pneumoniae*, medication can stop 72 h after the patient maintains normal temperature. For severe pneumonia, in addition to the completion of the effective, timely, and appropriate anti-infection treatment, nutrition supporting therapy and respiratory secretion drainage are very important.

13.3.3.2 Hospital-Acquired Pneumonia (HAP)

The key point for HAP initial empirical antibiotic therapy is whether the patient has the risk factors for MDR pathogen infection (Chinese Thoracic Society 1999). These factors include the use of antibiotics in the past 90 days and hospitalization for 5 days or longer. The frequency of antibiotic resistance is higher when the patient has been treated in community or other medical institutions. Risk factors for health care-associated pneumonia (HCAP) are hospitalization for more than 2 days due to the exacerbation of infection within 90 days, IV therapy administered at home (including antibiotics), dialysis continuously within 30 days, trauma treatment at home, the presence of family members infected with multidrug-resistant pathogens, and immunosuppressive diseases and/or immunosuppressive therapy.

If the patient has early onset HAP, ventilator-associated pneumonia (VAP), or HCAP with no risk factors for MDR pathogens, the common pathogens include *S. pneumoniae*, *H. influenzae*, *S. aureus*, and Enterobacteriaceae (such as *E. coli*, *K. pneumoniae*, *Proteus*, and *Serratia*). The initial empirical choice of antibiotics includes ceftriaxone, levofloxacin, moxifloxacin, ciprofloxacin, ampicillin/sulbactam, or ertapenem.

For the patients with risk factors for MDR pathogens of HAP, VAP, and HCAP, common pathogens include *P. aeruginosa*, *K. pneumoniae* that produce extended-spectrum β-lactamase (ESBL), *Acinetobacter* species, and other bacteria. The initial empirical antibiotic should be anti-*Pseudomonas* cephalosporins (cefepime, ceftazi-

dime), carbapenems (imipenem, meropenem), or β-lactam/β-lactamase inhibition agents (piperacillin/tazobactam). Anti-*Pseudomonas* quinolones (ciprofloxacin or levofloxacin) or aminoglycosides (amikacin, gentamicin, or tobramycin) can be used together. If methicillin-resistant *S. aureus* (MRSA) is suspected, linezolid or vancomycin can be added. If *L. pneumophila* is suspected, macrolides or fluoroquinolones can be added.

Once HAP is suspected in the clinic, and after the specimen is collected for bacterial culture, empirical antibiotic treatment should start as soon as possible (1 h later). Combination therapy must be used for the initial treatment of MDR pathogens to ensure broad-spectrum coverage and reduce the possibility of inappropriate initial empiric antibiotic therapy. Note that if the patient had recently used one kind of antibiotic, the same one should be avoided in empirical treatment to avoid development of antibiotic resistance. All treatments must be based on the local antibiotic resistance situation for choosing the drugs and establishing the appropriate empirical treatment program.

Adequate doses of antibiotics must be used for severe HAP or VAP patients to ensure maximum efficacy (Chronic Obstructive Pulmonary Disease Study Group of the Chinese Thoracic Society 2007). For adult patients with good renal function, the commonly used full doses are as follows: for cefepime and ceftazidime, 2 g every 8 h (q8h); for meropenem, 1 g q8h; for imipenem, 0.5 g q6h or 1 g q8h; for piperacillin/tazobactam, 4.5 g q6h; for ciprofloxacin, 400 mg q8h; for amikacin, 20 mg/kg daily; levofloxacin is 750 mg daily. Patients who haven't changed their antibiotic in the past 72 h can stop antibiotic drug treatment if specimens from their lower respiratory tract are culture negative. Drug adjustment should be made according to the culture results of the specimen of the lower respiratory tract and the clinical effect. For HAP, VAP, or HCAP patients who have received appropriate initial treatment with no evidence of infection by non-fermentative gram-negative bacteria and no complications, a short-course treatment (7–8 days) is recommended if the initial treatment went well. If the patient responds to aminoglycosides present in the combination drugs, this kind of medication should be stopped after 5–7 days.

13.3.3.3 Pneumonia in the Immunocompromised Host

There are numerous pathogens infecting the lung of the immunocompromised host, which increases opportunities for special pathogen infections. As a result, special pathogen infections such as viruses, fungi, and *Pneumocystis jirovecii* should be closely monitored in addition to mycobacteria and bacterial infection.

Bacterial Infections

For the acute onset nidus (3–5 days) with local alveolar infiltration, the main infection pathogen is bacterial. Empirical antibiotic treatment should refer to the CAP and HAP program described above.

P. jirovecii Pneumonia (PCP)

For patients presenting with diffuse pulmonary alveoli and interstitial infiltration accompanied by hypoxemia in occult or subacute onset, *P. jirovecii* may be the causative pathogen. The preferred treatment is sulfamethoxazole (100 mg/kg/day) and trimethoprim (20 mg/kg/day) taken orally or by intravenous drip. The general course of treatment is 14–21 days. Caspofungin will be used if the treatment is ineffective (the first dose is 70 mg, followed by 50 mg daily, by slow intravenous infusion).

Cytomegalovirus Pneumonia

There is no specific clinical feature of Cytomegalovirus (CMV) pneumonia other than the first symptoms of fever, cough with scanty sputum, dyspnea, and hypoxemia. The main imaging manifestation is interstitial pneumonia, which is characterized by the nonconformity between the clinical symptoms and its imaging performance. There is no abnormal image or only thickened blurred lung marking in the early chest X-ray. Then distinct interstitial pneumonia appears in both lungs, and after active antiretroviral therapy, clinical symptoms improve significantly and chest X-ray shows slow absorption of lesions. The best choice is ganciclovir alone or in combination with intravenous immunoglobulin (IVIG), or CMV immunoglobulin. The starting dose of ganciclovir is 5 mg/kg 2 times a day for 14 days, then once a day for an additional 7 days. The course of treatment is usually 21 days.

Invasive Pulmonary Mycosis

Invasive pulmonary mycosis refers to acute or chronic histological damage caused by a direct colonization of the lung or bronchial by fungi. Common pathogens are *Candida*, *Aspergillus*, *Cryptococcus neoformans*, *Zygomycetes*, and *Penicillium marneffei* (mainly seen in Southeast Asia and southern China). Because *Candida* pneumonia is rare, antifungal treatment will generally not be adopted if *Candida* has been cultured from sputum.

The typical progression of invasive pulmonary mycosis is as follows: in the early period (0–5 days) there is inflammation shadow, with mist-like oozing around it (shadow or halo sign caused by bleeding around the lesion). From day 5 to day 10, there is gas chamber consolidation in the inflammatory lesions with visible air bronchogram. From day 10 to day 20, the lesion develops to a half-moon shaped translucent zone (air half sign, caused by coagulation necrosis and pulmonary embolism) and it can deteriorate to complete necrosis cavity, most of which is single onset. The lesion sizes are variable and the distribution has no obvious features. Drugs for treatment could involve voriconazole, itraconazole, caspofungin, or micafungin, and two of them can be combined if necessary. Imaging of pulmonary cryptococcosis often has nodules or mass shadow under pleural in unilateral or bilateral lung

fields, and can be single or multiple onset, with a diameter of l–10 cm and smooth edges or fuzzy or with small burrs. Often, there is a cavity formed, and the wall is relatively smooth with uniform and very neat low-density shadow in the nodular shadow image. It is very important in pulmonary cryptococcosis diagnosis to note the presence of nodules or masses with smooth low-density necrosis areas or cavities, especially in multiple appearances which is usually what happens in patients with healthy immune systems. In contrast, the main progression in the immunocompromised host shows parenchymal infiltration, which is hard to distinguish from pneumonia caused by other pathogens. Amphotericin B and flucytosine can be used together or fluconazole can be used for treatment, with the treatment course lasting from 8 weeks to 6 months. Itraconazole could be used orally for patients who are not coinfected with meningitis. In pulmonary mucormycosis cases, the important symptoms for diagnosis are hemoptysis and chest pain with no other signs. Its early imaging shows bronchial pneumonia, with rapid integration into a large consolidation. This is often seen with a formed cavity and a wedge-shaped shadow which can be seen at the bottom near the pleura (if there is a large pulmonary vessel embolism). This is valuable for diagnosis. Currently, amphotericin B is the most effective medicine in the clinic (the dose is 0.5–1.5 mg/kg/day, with the total amount of 2.5–3.0 g for the course of treatment). It is used in combination with flucytosine.

P. marneffei infection (Penicilliosis) manifests with fever, anemia, skin lesions, cough, hepatosplenomegaly, and generalized lymph node swelling, which is not specific in imaging and is often misdiagnosed as TB. Amphotericin B is used for treatment, with a switch to itraconazole oral therapy 2 weeks later. Immunesuppressed hosts require long-term use of itraconazole.

13.3.3.4 Aspiration Pneumonia

The possibility of aspiration pneumonia should be considered in elderly patients with a history of consciousness disorder or difficulties in swallowing who have respiratory symptoms followed by pulmonary infiltrated shadow. Diagnosing correctly and taking appropriate measures for the swallowing-impaired patient can reduce the incidence of aspiration pneumonia. The following factors are used to evaluate oropharyngeal dysphagia in the clinic: abnormal velopharyngeal reflex (palatal reflex and pharynx reflex), coughing when eating, and a change in sound after swallowing. Treatments are different according to the way the pneumonia is acquired. Treatments for CCFAP, HAP, and CAAP consist of the empirical treatment programs described above. Anaerobic treatment should be considered as well. Penicillin combined with metronidazole, clindamycin, β-lactam/β-lactamase inhibitors, or carbapenems can be used for anaerobic treatment. The general course for treatment is 7–10 days, and the time could be prolonged to 14–21 days or even weeks to months if the patient is coinfected with necrotizing pneumonia or has a lung abscess.

13.3.3.5 Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

Once COPD symptoms are exacerbated, especially with the aggravation of cough and purulent sputum, active antibiotic therapy should be adopted. Antibiotic selection should be based on the patient's lung function and common pathogens, and the prevalence of pathogenic bacteria and drug resistance of the area should be taken into account to select sensitive antibiotics. The course of treatment is 3–7 days.

Antibiotics Indications for AECOPD

Antibiotics should be considered in cases of COPD exacerbations with three principal symptoms of increase in sputum volume, increase in sputum purulence, and increase in shortness of breath, or with two principal symptoms when one is an increase in sputum purulence or when the patient requires mechanical ventilation (either noninvasive or invasive).

Risk Factors for *P. aeruginosa* Infection of COPD

Patient risk factors for *P. aeruginosa* include recent hospitalization, frequent antibiotic treatment history (using four courses of antibiotics in the past year), severe COPD deterioration, having isolated *P. aeruginosa* in a previously acute exacerbation period or contracted *P. aeruginosa* clone during a stable period.

Application of Antibiotics

The Chinese Society of Respiratory Disease recommends treatment depending on lung function and the infectious pathogen(s) present (Chronic Obstructive Pulmonary Disease Study Group of the Chinese Thoracic Society 2007).

1. For Grade I (with forced expiratory volume in 1 s, FEV_1, at ≥80 % of the predicted volume) and Grade II (50 % ≤ FEV_1 < 80 % of predicted volume) COPD acute exacerbations, the main pathogens are *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*. Antimicrobial drugs for treatment may include oral penicillin, β-lactam/β-lactamase inhibitor (amoxicillin/clavulanic acid), macrolides (azithromycin, clarithromycin, roxithromycin etc.), the first- and second-generation cephalosporins (cefuroxime, cefaclor), doxycycline, levofloxacin, and so on.
2. For Grade III (30 % ≤ FEV_1 < 50 % predicted volume) and Grade IV (FEV_1 < 30 % predicted volume, or patients with chronic respiratory failure) COPD acute exacerbations with no risk factors for *P. aeruginosa* infection, the main pathogens are *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *K. pneumoniae*, *E. coli*,

and *Enterobacter* spp. Antimicrobial drugs for treatment include intravenous β-lactam/β-lactamase inhibition agents, second-generation cephalosporins (cefuroxime), third-generation cephalosporins (ceftriaxone, cefotaxime, etc.), and respiratory quinolones (levofloxacin, moxifloxacin).

3. In Grade III (30 % ≤ FEV_1 < 50 % predicted volume) and Grade IV (FEV_1 < 30 % predicted volume, or patients with chronic respiratory failure) COPD acute exacerbations with risk factors for *P. aeruginosa* infection, the main pathogens include those in group 2 previously described and *P. aeruginosa* bacteria. Antimicrobial drugs include intravenous injection β-lactam antibiotics (such as ceftazidime, cefepime, piperacillin/tazobactam, cefoperazone/sulbactam, imipenem, and meropenem) with anti-*Pseudomonas* activity. Aminoglycosides and quinolones (ciprofloxacin, etc.) can be combined if it is necessary.

13.3.3.6 MDR Infection

As drug-resistant bacterial infections increase, drug susceptibility results become more and more important in choosing treatment. The most common clinical MDR pathogens are *P. aeruginosa*, *Acinetobacter*, ESBL-producing *Enterobacteriaceae*, and MRSA. Combined therapy, mainly using β-lactam combined with aminoglycosides, is recommended for *P. aeruginosa*. Aminoglycosides can be replaced by fluoroquinolones (mainly ciprofloxacin or levofloxacin). The most effective drugs for *Acinetobacter* treatment include carbapenems, sulbactam, tigecycline, and polymyxins B and E. When isolating ESBL-producing *Enterobacteriaceae*, the third-generation cephalosporin monotherapy should be avoided. For *Enterobacter* bacteria, the most effective drugs are carbapenems. Large-scale, multicenter trials have proved the curative effect of linezolid and vancomycin is equal in MRSA treatment. For patients with renal insufficiency or receiving other nephrotoxic agents, linezolid is recommended. In addition, inhaled antibiotics are valuable as an adjuvant therapy for VAP caused by MDR pathogens. The course of treatment depends on the patient's infection pathogens, severity degree, background diseases, and clinical response to treatment.

13.3.3.7 Treatment Failure

Antibiotic treatment can fail for many reasons. The patient could be misdiagnosed and/or the infectious pathogen(s) misidentified or secondary infection undetected. External sources of infection such as ventilator-related contamination can be persistent. Medication failures can occur due to drug resistance, limitations due to adverse drug reactions, and/or insufficient respiratory drug concentration due to drug or anatomical factors. The pulmonary infection may spread outside the lung. The patient's own immune defense may cause damage, including systemic inflammatory response, leading to acute lung injury or even multiple organ failure.

In cases of treatment failure, the following steps should be adopted: establish a reliable etiological diagnosis, referring to drug sensitivity and/or blood concentration to develop or adjust treatment; eliminate sources of contamination to prevent cross-infection; and prevent, treat, or eliminate other factors that might cause or aggravate lung injury.

13.3.4 Respiratory Failure

Respiratory failure is a physiological and metabolic disorder syndrome that is caused by pulmonary ventilation dysfunction and/or external disease of TB. The direct reason for respiratory failure is that the body cannot maintain effective gas exchange. Respiratory failure is defined when the patient, at rest and breathing air at sea level pressure, has arterial oxygen pressure (PaO_2) lower than 8 kPa (<60 mmHg), with or without carbon dioxide partial pressure ($PaCO_2$) higher than 6.67 kPa (50 mmHg). There is always a process as respiratory failure develops, especially for chronic respiratory failure. Respiratory function may be reduced gradually. If the external respiratory dysfunction causes elevated $PaCO_2$ or decreased PaO_2 and does not reach the standards above, or at rest blood gas values are normal with no obvious clinical symptoms, but PaO_2 decreases apparently or $PaCO_2$ increases only if physical load increases, this state is often called respiratory insufficiency. Once pulmonary TB with concurrent (chronic) respiratory failure is exacerbated acutely by other factors, coma, shock, and life-threatening can occur. As it is reported, 93 % of the patients who died of pulmonary TB with respiratory failure died in transit to the ICU (Lee et al. 2003). The main principles for treatment of TB combined with respiratory failure include keeping the respiratory tract unobstructed, correcting hypoxia and reducing carbon dioxide retention, correcting acid–base imbalances and electrolyte disturbance, initiating/continuing anti-TB therapy, treating inducing factors, preventing complications, and supporting good nutrition.

13.3.4.1 Airway Control

Attention should be paid to posture and basic airway management: head-tilt/chin-lift and jaw-thrust maneuvers should be performed to prevent the tongue from falling back and obstructing the airway.

If the patient loses the function of sputum clearing, clearing the secretions of the mouth, pharynx, larynx, and lower respiratory tract is important. Bronchoscopy can be used for removing the large amount of deep accumulated secretions which are not easy to expel.

The discharge of secretions should be increased. Expectorant can be used if the patient has good mucociliary clearance. Pay attention to the airway humidification and the dilution of sputum (whether sputum is easy to cough or aspirate is the sign

for humidification), and encourage the patient to cough with good posture to promote drainage.

The bronchi should be expanded, and airway inflammation and edema should be reduced. Drugs such as β-receptor stimulants, anticholinergic agents, and methylxanthines may be chosen according to the role of drug and treatment response for patients. It is recommended that aerosols be inhaled into the lung, but if the airway is severely occluded, intravenous injection should be given first.

Artificial airways should be built by nasotracheal intubation or orotracheal intubation if necessary. Nasotracheal intubation is usually more comfortable for the patient, and the airway can be fixed easily, but its disadvantage is that it may cause nasosinusitis or tympanitis. The advantage for orotracheal intubation is that it can be set up easily and requires less equipment. To reduce complications and improve the success rate of recovery, intubation is recommended before patients have irregular breathing, choking, or fall into coma. If the patient requires intubation for more than 3 weeks, tracheotomy is recommended.

13.3.4.2 Oxygen Therapy

High concentrations of oxygen may be given to Grade I respiratory failure patients to increase PaO_2 rapidly. FiO_2 can be adjusted at a beginning reading of 0.4, with the PaO_2 target of 60–80 mmHg.

In Grade II respiratory failure patients, adopt controlling oxygen therapy to prevent respiratory depression. Administer 24–26 % oxygen as long as $PaCO_2$ does not increase by more than 10 mmHg and the patient is conscious. The oxygen concentration may increase, but not more than 30–35 %. For the patient receiving long-term oxygen therapy greater than 15 h daily, the target PaO_2 is 50–60 mmHg with a $PaCO_2$ increase of less than 20 mmHg.

It is important to pay attention to the adverse effects of oxygen therapy. The common adverse reactions include suppressed ventilation (common in chronic Grade II respiratory failure patients) and oxygen toxicity. Oxygen toxicity can affect the lungs (injured epithelial cells of the alveoli cause pulmonary edema) and the central nervous system (manifested as trembling, convulsions, and seizures). It is recommended that patients inhale pure oxygen for less than 24 h, with 70 % oxygen used less than 2 days, and 50 % oxygen used less than 5 days. Note that as the oxygen content of inhaled air is increased and rapidly absorbed by blood exchange, the reduced volume of nitrogen remaining may not be sufficient to keep the lungs inflated and absorption atelectasis can occur.

13.3.4.3 Increasing Ventilation and Reducing Carbon Dioxide Retention

Carbon dioxide retention is one of the principal pathophysiological changes caused by alveolar hypoventilation, and can induce a series of clinical manifestations. Clinically, increasing the amount of alveolar ventilation can effectively reduce CO_2

retention. However, because of the differences in the pathophysiological basis of TB patients combined with respiratory failure, the strategies and measures for increasing ventilation are different. They are summarized below.

Application of a Respiratory Stimulant

Application of a respiratory stimulant is controversial. It may be worth trying for the severe TB cases, especially elderly patients with bronchus and lung structural damage and/or extensive lesions such as cavity and bullae. Mechanical ventilation in these kinds of patients may lead to more complications and higher failure rate.

Conservative therapy can be used for the conscious patient who is hemodynamically stable with $PaCO_2$ < 60 mmHg, oxygenation index between 200 and 300 mmHg, $PaCO_2$ between 50 and 60 mmHg, and blood pH value between 7.30 and 7.35. When using respiratory stimulants, secretion drainage and control of airway spasms should be noticed, and great attention should be paid to patient consciousness and $PaCO_2$ after use. If $PaCO_2$ does not drop or the patient loses consciousness, mechanical ventilation should be used instead.

Mechanical Ventilation

Mechanical ventilation technology is the most important clinical tool for treatment of respiratory failure; however, TB, bullae, and hemoptysis are considered contraindications. Mechanical ventilation may cause the spread of pulmonary TB, making treatment more difficult. Studies have shown that among patients using mechanical ventilation for pulmonary TB combined with respiratory failure, the mortality rate is up to 60 %, which is similar to ARDS and twice that of pneumonia caused by respiratory failure (Lee et al. 2003; Rollas et al. 2015). Therefore, it is necessary to explore a set of effective strategies and programs to guide the application of mechanical ventilation in the treatment of pulmonary TB with respiratory failure. Mechanical ventilation can be either invasive or, if external, noninvasive positive pressure ventilation (NPPV). Many scholars have suggested using a flexible selection scheme: for patients with respiratory failure who have no contraindications for NPPV, NPPV can be implemented and, according to patient response, continued or halted in favor of invasive ventilation. The key point of using this strategy is rationally to master the indications of NPPV and invasive ventilation as well as when to change from NPPV to invasive ventilation. NPPV is widely used clinically because it doesn't require intubation or incision and thus avoids complications of artificial airways. NPPV can also reduce the need for sedatives, as it does not affect normal swallowing, eating, or talking. It can help to preserve the air temperature and humidity of the lungs and minimize coughing. It can also be used intermittently and patients can be taken offline easily. The clinical effectiveness of NPPV should be evaluated 1–2 h after treatment. Signs of clinical improvement include a $PaCO_2$ decrease > 16 %, pH > 7.30, and an oxygenation index > 164 mmHg. There are always a certain percentage

of failures for NPPV treatment. Therefore, for patients with no improvement after NPPV treatment and who have indications of endotracheal intubation, prompt emergency intubation must be considered. Additionally, in the case of irritability or loss of consciousness, inability to clear secretions or tolerate the connection method, hemodynamic instability, oxygenation deterioration, or increase in carbon dioxide retention, intubation should be done as soon as possible.

13.3.4.4 TB Conditions and Ventilation Strategies

There are several common situations for TB patients with respiratory failure; each has their own ventilation strategies (Xie and Liu 2008; Physiology and Intensive Care Medicine Group of the Chinese Thoracic Society 2009).

Severe TB Patients with Bronchial Pulmonary Structural Damage

Severe TB patients with bronchial pulmonary structural damage often have extensive lung lesion cavity, bullae, etc., and may have concurrent infection. These patients easily lose weight, are malnourished, and are prone to respiratory muscle fatigue. Meanwhile, there is often compensatory emphysema in the so-called "healthy" lung tissue. In addition, TB bronchiectasis and pleural thickening are often combined. Most of these patients are elderly and may have TB-associated chronic obstructive pulmonary disease, pulmonary heart disease, and so on. There are several reasons for respiratory failure, not only pump failure, such as thorax, pleural changes, respiratory muscle fatigue, but also lung failure such as airway obstruction, lung tissue lesions, and pulmonary circulation disorders. Mechanisms of respiratory failure include both restrictive hypoventilation and obstructive hypoventilation. There is not only an increase in the functional shunt induced by part of the pulmonary alveoli hypoventilation, but there is also an increase in functional dead space due to the induction of pulmonary alveoli blood hypoperfusion. Both diffusion impairment and anatomic shunt increase. Therefore, such patients usually have both disturbed ventilation and ventilatory disorders, showing type II respiratory failure, chronic respiratory failure, acute exacerbation of chronic respiratory failure, and so on. The preferred strategy is to try to adopt conservative and noninvasive ventilation. Forceful anti-TB treatment, beginning as early as possible, is effective to prevent TB lesions spreading during mechanical ventilation. After the acute phase, patients can receive long-term home NPPV therapy if needed.

Noninvasive ventilation can be used according to the patient's situation as long as the patient is conscious, has stable hemodynamics, can expectorate independently, and following conditions are met: $PaO_2 < 60$ mmHg, oxygenation index between 150 and 200 mmHg, $PaCO_2$ at 50–60 mmHg, and blood pH is between 7.20 and 7.30. Continuous positive airway pressure (CPAP) mode can be used for type I respiratory failure, and bi-level positive airway pressure (BiPAP) mode can be used for type II respiratory failure. Initial inspiratory pressure airway pressure

(IPAP) ranges from 6 to 25 cmH_2O until the patient can no longer tolerate it. The expected tidal volume is 6–8 mL/kg; expiratory pressure airway pressure (EPAP) generally begins from 2 cmH_2O, and the oxygen flow is adjusted to maintain transcutaneous oxygen saturation at more than 90 %. Adjust the IPAP and EPAP at any time according to the patient situation. According to patient tolerance, ventilation time is set to 2 h at a time, three to four times a day, according to patient tolerance, until 24 h with continuous application is reached. Reassess the patient regularly and consider repeat arterial blood gas analysis.

Many conditions suggest that noninvasive ventilation has failed, and a switch to invasive ventilation is required. Main indications of failure include respiratory arrest, loss of consciousness with apnea, severe hemodynamic instability (heart rate < 50 beats/min with unconsciousness, and/or systolic blood pressure < 70 mmHg), and required sedation to control agitation. Secondary failure indications are breathlessness, increasing respiratory rate > 35 breaths/min, PaO_2 < 45 mmHg or oxygenation index < 150 mmHg, $PaCO_2$ increased > 20 % or $PaCO_2$ > 60 mmHg, blood pH value < 7.20, and a change in the state of consciousness.

In invasive mechanical ventilation conditions, lung protective ventilation strategies are adopted such as applying ventilation with lower tidal volumes to maintain the airway platform pressure below 30 cmH_2O and using the mode of pressure control or pressure support to avoid barotrauma. The desired parameters are tidal volume of 6–8 mL/kg, respiratory rate of 15–20 breaths/min, inspiratory flow rate of 40–80 L/min, and an oxygen concentration of 0.6–1 (adjusted according to arterial blood gas analysis results). The expiration time should be extended so the inspiratory-to-expiratory time (I:E) ratio is <1:2. Try to maintain the airway platform pressure at ≤30 cmH_2O; positive end-expiratory pressure (PEEP) should usually be no more than 5 cmH_2O.

Immunosuppression in TB Combined with Secondary Lung Infection

Long-term use of immunosuppressive drugs can cause secondary lung infection and respiratory failure. Most of these patients have more critical illness, more rapid disease progression, and higher mortality rate. It is recommended to use the ICU exclusive NPPV respirator that can precisely adjust the inspired oxygen concentration and choose the oral-nasal mask with a better seal to carry out noninvasive ventilation. Generally, invasive mechanical ventilation mode is not recommended, because it can facilitate the onset of VAP.

Bronchopleural Fistula

A bronchopleural fistula is an opening connecting between the bronchus and the pleural space. TB patients are prone to suffer bronchopleural fistula because of secondary surgery, primary lung structural damage, or pulmonary barotrauma by mechanical ventilation. Mechanical ventilation should be used after taking all kinds

of reasonable measurements to reduce leakage and reduce the possibility of further damage. To implement a permissive hypercapnia strategy, apply lower respiratory rate, lower tidal volumes, and higher inspiratory flow (70–100 L/min) to reduce the inspiratory time and lower PEEP. Patients may be put under deep sedation, and even muscle relaxants can be used to avoid putting the patient in a position that could exacerbate leakage. Use the minimum chest tube attraction to maintain lung expansion, and take strong measures to heal the expiratory flow obstruction caused by bronchial spasms and other reasons. Measurements such as lung ventilation or thoracic drainage catheter plus PEEP can be used if necessary.

TB and AECOPD

NPPV is the preferred treatment for AECOPD patients to support their respiratory system. NPPV is effective for the TB patient with AECOPD and blood pH between 7.25 and 7.35 and $PaCO_2 > 45$ mmHg. For the patient with $PaCO_2 > 45$ mmHg, pH ≥ 7.35, NPPV is suggested for use in the early stage to avoid exacerbating illness. BiPAP mode is recommended. There should be more than 6 cmH_2O D-value between IPAP and EPAP to improve the patient's alveolar ventilation, relieve respiratory muscle fatigue, and correct the hypercapnia. The recommended EPAP level is between 4 and 6 cmH_2O and the maximum should be less than 8 cmH_2O so as not to aggravate lung dynamic hyperinflation (DH). For the patient with severe AECOPD, endotracheal intubation should be actively used for invasive mechanical ventilation treatment in the following cases: pH < 7.25, significant hypoxemia (PaO2 < 45 mmHg) and hypercapnia (PaCO2 > 80 mmHg), unconsciousness, unstable hemodynamics, a large amount of airway secretions, and/or the patient cannot tolerate NPPV treatment or has little or no remission after 2 h of NPPV treatment. The principles for mechanical ventilation are lower tidal volumes (5–7 mL/kg), slower frequency (12–15 times/min), and longer expiration time (I/E < 1:1.5). $PaCO_2$ can be slightly higher than normal, and, in principle, PEEP level should not be too high (70–80 % of the static intrinsic PEEP is allowed). Assisted ventilation (PSV + PEEP, SIMV + PSV + PEEP) mode should be adopted as soon as possible after the patient's condition is stable. Extubation (usually after intubation for 4–6 days) should be executed promptly (based on pulmonary infection control or respiratory physiological parameters) in order to effectively prevent VAP and ventilator-dependence. For COPD patients who are at the stage of rehabilitation, and satisfy the following conditions, NPPV treatment should be applied especially at night: when accompanied with fatigue, shortness of breath, lethargy, and other symptoms; when having abnormal gas exchange ($PaCO_2 \geq 55$ mmHg or is between 50 and 55 mmHg, $SaO_2 < 88$ % in the case of oxygen applied) and the situation continues for more than 10 % of the monitoring time; when having bad effects from bronchodilators and/or hormones, oxygen, and other medical treatment; for patients with moderately severe obstructive sleep apnea who are unresponsive to CPAP treatment.

Bronchial Asthma with Pulmonary TB

Bronchial asthma patients are more prone to TB because of their long-term use of corticosteroids and respiratory failures often related to acute severe attacks of asthma. Routine NPPV treatment is not recommended for severe asthma patients, and when NPPV is used for bronchial asthma, patients should be monitored carefully. Mechanical ventilation is the final effective means for treating severe asthma in TB patients. For some severe asthma patients whose main symptom is solely hypoxemia, application of CPAP can effectively relieve respiratory muscle fatigue and improve oxygenation. Application of BiPAP can relieve respiratory distress rapidly, promote carbon dioxide emissions, and improve respiratory function. Invasive mechanical ventilation should use the strategy of lower tidal volumes (6–8 mL/kg), lower frequency (10–15 times/min), and longer expiration time (I/E < 1:2); sedative drugs are required for patients to coordinate with treatment. PEEP levels should not be too high; generally about 5 cmH_2O is acceptable.

13.3.4.5 Balancing the Acid–Base Ratio and Solving the Electrolyte Turbulence Problem

When suffering from respiratory acidosis, resolution can come by increasing ventilation, and inhaling a small amount of alkali when the pH < 7.20. The main reason for respiratory acidosis with metabolic acidosis is lactic acidosis caused by hypoxia, which can be treated by ventilating, increasing oxygen delivered to tissue, and adding an appropriate amount of alkali. Most cases of respiratory acidosis with metabolic alkalosis are iatrogenic (such as excessive ventilation and diuretics). Symptoms such as low potassium, low chloride, and low sodium are common in electrolyte imbalance, and it is important to remember to replenish electrolytes. Water balance is also important. Excess fluid intake induces or aggravates cardiac insufficiency. Conversely, insufficient fluid is likely to lead to sputum drainage problems which aggravate airway obstruction.

13.3.4.6 Treatment of Predisposing Factors and Basic Diseases

There are many factors that could induce respiratory failure once the respiratory tract is infected. Treatments of pathogens vary according to their different basic diseases, different risk factors, and different pathogenic microorganisms. Moreover, treatment of basic diseases is also very important. For the patient with respiratory failure caused by severe TB who has bronchial pulmonary structural damage, strong anti-TB treatment at an early stage can effectively prevent spread in mechanical ventilation. This could directly impact the prognosis of patients. Goals for the TB patient with COPD are mainly for the treatment of chronic airflow obstruction, reduction of airway inflammation, and increase of secretions from the airway. For the patient with combined bronchial asthma, the key point is asthma control.

13.3.4.7 Preventing Complications

Diuretics and vasodilators could be used appropriately for heart failure, but cardiac glycosides must be used cautiously. Application of β blockers and antiarrhythmic drugs is avoided for arrhythmia. Drugs which could impair liver function are avoided, so as not to affect the normal application of anti-TB drugs. Complications such as gastrointestinal bleeding, shock, and DIC should be treated immediately. A key way to prevent multiple organ failure is to master the right time and method of oxygen therapy and mechanical ventilation to improve ventilation and avoid hypoxia. It is important to determine and treat hypotension promptly to avoid organ hypoperfusion. Also, note that TB is a chronic wasting disease. TB patients with respiratory failure can easily develop anemia, which should be corrected in order to improve blood capacity for oxygen and increasing the oxygen supply.

13.3.4.8 Nutritional Support

The majority of pulmonary TB patients are malnourished, which can make active TB progress and worsen. Protein–energy malnutrition (usually manifested as marasmic kwashiorkor type) affects the structure and function of the respiratory muscle, reduces ventilatory drive capability, and seriously affects the body's immune defenses. This has a negative impact on prognosis; TB is recurrent and hard to heal. In the early stage, nonprotein calories should be low, which may be increased to 30–35 kcal kg^{-1} d^{-1} after the situation is stable. For some patients with severe malnutrition problems who can not be offline, calories should be increased according to the patient tolerance to correct hypoproteinemia and malnutrition. The minimum ratio of glucose and fat calories is 50:50, the ratio of calories and protein should be 100 to 150:1, the protein intake should be 1.5–2.0 g kg^{-1} d^{-1} (Tayek 2002; Kreymann et al. 2009; Chen et al. 2011; Grau Carmona et al. 2011; Elke et al. 2014)

Vitamins and trace elements should be added to balance the electrolytes with special attention to the elements which could affect respiratory muscle function (such as potassium, magnesium, and phosphorus). Because of gastrointestinal disorders and anorexia, TB patients have reduced nutrient intake, resulting in an anabolic reduction. Meanwhile, *M. tuberculosis* will use the body's protein for its metabolism, causing fever, night sweats, weight loss, and other consumable changes, and leading to increased catabolism, decreased fat storage, and loss of lean body mass. When the body temperature increases 1 °C, metabolic rate will increase 13 % (Tan and Li 2000). Nitrogen and amino acids could get lost from sweat. Therefore, TB patients have a relatively higher catabolism rate, and their energy consumption is higher than that of healthy people. The basal metabolic rate (BMR) could increase 50–150 %. In severe stress, the catabolism rate is significantly higher than the anabolism rate, resulting in increased protein loss and muscle tissue loss. This causes skeletal muscle atrophy and negative nitrogen balance, causing hypoproteinemia and decreases immune function, which increases the infection rate and mortality. Glycometabolism is another metabolic disorder when the body is suffering stress.

The symptoms include high blood sugar, decreases in glucose oxidation and utilization rates, insulin resistance, and an increase in gluconeogenesis. Meanwhile, the energy intake reduces and histanoxia can develop, causing increased lactic acid which leads to acidosis. Among the 88.6 % of TB patients with malnutrition, 58.8 % have caloric malnutrition, 25.2 % have mixed malnutrition, and 4.6 % have protein malnutrition (Tan et al. 2005). Weight loss is a main characteristic for TB patients.

Increasing Caloric Intake

TB is a chronic wasting disease. Patients require more energy than healthy people. The general requirement is 30 kcal kg^{-1} of body weight, with the total intake about 2000 kcal each day. For a light manual laborer, 40 kcal kg^{-1} of body weight and about 2400 kcal per day are needed.

Increasing Protein Intake

Patients need more protein not only because of their high consumption, but also due to the benefit of protein for tissue repairing, lesion healing, and body recovery. TB patients need to have an intake of 1.2–1.5 g protein per kilogram of body weight daily, with the total intake of 80–100 g each day, 50 % of which are high-quality proteins such as meat, poultry, seafood, eggs, milk, and soy products.

Increasing Vitamin Intake

Vitamins A, B, C, and D should be supplemented first. Vitamin A can enhance the body's immunity, B vitamins could improve appetite, and vitamin B6 may relieve side effects caused by the use of isoniazid. Vitamin C will help lesions healing and hemoglobin synthesis, and vitamin D can promote calcium absorption. Fresh fruits and vegetables are the main source of vitamins. In addition, milk, eggs, and offal are rich in vitamin A. Yeast, peanuts, beans, and lean meats are rich in vitamin B6.

Calcium and iron should be supplemented in TB patients. Calcium is the raw material for TB calcification. Patient should drink 250–500 g of milk daily, which contains plenty of good calcium. Patients having hemoptysis or hematochezia should add iron, which is an essential raw material for hemoglobin manufacture.

In summary, during the treatment of TB, patients have to be given adequate nutrition, to enhance their immune function and reduce the negative oxygen balance in order to repair the body. Nutritional therapy is mainly focused on energy and protein supplements. In the process of energy supplementation, pay attention to the ratio of sugar and fat so as not to aggravate the liver and lung burden due to excessive sugar. The combined use of fat emulsion and glucose could provide more energy, thereby reducing protein breakdown for energy and improving nitrogen balance. Branched

chain amino acids and other essential amino acids should be supplied to enhance the body's protein levels, reducing albuminolysis, to promote nutritional recovery.

Diabetes mellitus, silicosis, and lung structural damage are the main predisposing factors for pulmonary TB, and recurrent pulmonary infection can weaken the body immunity, inducing pulmonary TB. Given these factors, in the diagnosis and treatment of pulmonary TB with concurrent disease or damage, it is critical to treat the two diseases together. In the course of treatment, we should pay attention to nutritional support and reduce the occurrence of complications.

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Chapter 14
Surgery for Pulmonary Tuberculosis and Its Indications

Yu Fu, Hongjin Duanmu, and Yili Fu

14.1 History of Surgery for Pulmonary Tuberculosis patients

It has been almost 200 years since the development of pneumosurgery (Waldhausen et al. 1996). In 1821, Milton Anthony completed the first lung resectional surgery in the world without anesthesia (Brewer 1982). Pulmonary tuberculosis (PTB) surgery started in the late nineteenth century, during a mass outbreak of PTB and before the advent of antibacterial agents. At that time, the only way to cure PTB was to prescribe rest and nutrition, which meant conservative therapy such as sunbathing on the beach and taking vitamins. It is believed that the reason for the failure of this approach was that the lung continued working without break, complicating the healing from PTB. In surgery, the burden of the lung could be diminished and PTB might be cured. In 1822, Carson first proposed artificial pneumothorax technology. In 1873, Wilms (1913) reported paravertebral thoracoplasty. In 1879, Estlander first cured tuberculous empyema by cutting the costal bone and causing chest wall collapse (Krassas et al. 2010). In 1911, Stuertz performed phreniclasia with collapse treatment for curing PTB. It was a simple operation that making a small incision in

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the neck, crushing a section of the phrenic nerve with a ring clamp, and causing a short time paralysis. But permanent phrenic nerve paralysis was a serious risk that could interfere with lung function, so this procedure was abandoned. Since 1935, thoracoplasty became an increasingly performed operation. Alexander (1937) proposed aboral lateral thoracoplasty, which could reduce the death rate to 2 % or lower after the operation. As a result, he is credited as the father of modern thoracoplasty.

In 1937, Wang Datong from Peking Union Medical College Hospital completed a pulmonary resection for a bronchiectasis patient, which was the first case in China. Then this surgery was extended to PTB patients (Li 2006). In 1943, investigators for the first time made a detailed description of the blood vessels and bronchi of all lung lobes and named them, which provided the foundation for lung surgery anatomy (Pomerantz and Mault 2000).

In the 1940s and 1950s, it was learned that collapse treatment led to pathological changes in patients' bodies. As a result, fewer patients opted for collapse treatment. Finally, it was replaced by lung resection in conjunction with chemotherapy (Xin and Ge 1964). Even now, lung resection therapy remains the main method for PTB surgery. In the 1950s, PTB surgery constituted 82 % of all the lung resection operations at Shanghai Second Tuberculosis Hospital in China (Wu et al. 1959; Special Study Group for Tuberculosis in Shanghai 1960).

14.1.1 PTB Surgery and Chemotherapy

As new anti-tuberculosis (TB) drugs are developed, more reasonable chemotherapeutic programs are implemented. As a result, most PTB patients can be healed by chemotherapeutic treatment. In the 1970s, most patients with initial treatment could be cured through a reasonable chemotherapeutic program with rifampin. Fox et al. (1999) proposed that surgery was unnecessary except for patients suffering from complications beyond PTB. This suggested that medical treatment could take the place of surgery. However, the lack of new chemotherapy drugs over time combined with incomplete chemotherapy and/or patient compliance has led to an increased number of patients with drug-resistant and Multidrug-resistant TB (MDR-TB).

Drug-resistant and MDR-TB has become a growing problem. The challenges of MDR-TB treatment include long-term treatment, high cost, serious side effects, ineffective chemotherapy, low rate of healing, and a high rate of relapse, illness, and death. Because of the emergence of MDR-TB, curing PTB surgically became an option again. Surgery for PTB can not only reduce the bacteria quantity and shorten the time for medication treatment but also eliminate the source of TB immediately by reducing its spread. Lalloo et al. (2006) suggested that surgery for curing MDR-TB could prevent the bacterial spread and protect the healthy lung issue. In 2005, Takeda et al. reported that 17.6 % of 199 operations on PTB patients were MDR-TB related. The PTB surgery patients ranged in age from 2 years to 78 years; 60–70 % were male and 20–40 % were female (Pomerantz et al. 2001; Takeda et al. 2005). MDR-TB patients especially may benefit from surgery. According to the statistical analysis, 2–5 % of PTB patients need surgery today (Sung et al. 1999).

14.2 Indications for PTB Surgery

The primary requirement for PTB surgery is that the patient's condition is stable after medical treatment, with unresolved infection but absence of active and diffuse bacteria (Yan and Duanmu 2003). The indications for PTB surgery treatment are:

- After normal anti-TB chemotherapy, sputum bacteriological examination remains positive or is intermittently positive and the lung lesion is localized.
- Though sputum bacteriological examination is negative, there are irreversible changes such as tuberculous cavity, destroyed lung, atelectasis, or large bullae. Respiratory function could be improved by removing nonfunctioning lung tissue and balancing the ventilation-perfusion ratio.
- TB has been resolved or incompletely resolved, but there are some complications such as bronchiectasis, recurrent hemoptysis, tuberculous empyema, or cancer.
- The most important condition for PTB surgery is that the bacteria are sensitive to two or more anti-TB drugs. Surgery can remove infected tissue, but it cannot eliminate all the TB bacteria. That is why effective anti-TB treatment after surgery is essential. If the bacterial strain in the patient is not sensitive to two or more of the anti-TB drugs, surgery alone may be very dangerous. For MDR-TB and extensively drug-resistant (XDR) TB patients who responded poorly to anti-TB chemotherapy, surgery could be performed if conditions permit. The surgical success rate is very low for MDR-TB and XDR-TB patients, so performing surgery before the bacteria becomes MDR or XDR is important.
- It is important to make sure patients understand and accept the surgical risks and treatment program. PTB patients who need surgery do not need to have their TB confined to one lobe or one side of the lung. It does not impact the operation effect if the rest of the lung is under control. Shiraishi et al. (2004) have reported that of 30 MDR-TB patients, only 6 had no significant lesions in the other side of the lung. If the rest of the lung or contralateral lung lesion is stable, or fibrous or cord-like lesions change, it will not affect the surgical treatment of lung resection.

14.3 Contraindications for PTB Surgery

- Patients with poor cardiopulmonary function who cannot tolerate surgery.
- After surgery, there will still be active TB in the rest of the lung or the contralateral lung.
- There is active bronchial TB in the opening where the lobe is to be resected.
- The bacterial strain in the patient is completely resistant to first-line and second-line anti-TB drugs.
- The patient refuses surgery.

14.4 Preoperative Preparation

Like other thoracic surgeries, TB patients receiving a lung resection need preoperative cardiopulmonary function tests to ascertain whether surgery can be tolerated. In addition, bronchoscopy must be carried out before surgery to make sure that there is no bronchial TB in the opening where the lung will be resected. Bronchial TB is one of the most serious risks causing bronchial stump fistulas after surgery. If possible, surgery should be carried out after the bacterial culture and drug susceptibility test, in order to guide the postoperative anti-TB treatment. The most important preoperative requirement is regular anti-TB treatment for 3–6 months before surgery. Preoperative anti-TB treatment is directly related to postoperative mortality and complication rates. In general, surgery should be performed when the level of TB bacteria is lowest in the body. Shiraishi et al. (2004) reviewed 30 MDR-TB cases. Patient infections were resistant to a range of 2–9 drugs. Preoperative chemotherapy was given for 3 months with 3–6 drugs (including fluoroquinolones for 80 % of the patients) as appropriate given sensitivity testing results. Naidoo and Reddi (2005) reported 23 patients using second-line anti-TB drugs for at least 3 months prior to surgery. Orki et al. (2009) reported 55 patients receiving a range of 3–6 anti-TB drugs for 2–8 months before surgery. Mohsen et al. (2007) reported 23 MDR-TB patients receiving 4–6 drugs (according to their drug susceptibility test) for at least 3 months. Tang and Xiao (2003) believed that MDR-TB patients should take anti-TB chemotherapy for at least 2 months prior to surgery. TB patients, especially MDR-TB patients, may be malnourished because of their prolonged course and long-term consumption. Addressing the nutritional needs has also become an important part of preoperative preparation. If necessary, provide enteral or parenteral nutrition to patients 2–4 weeks before surgery to reduce complications.

14.5 Methods of PTB Surgery

There are two types of methods used in TB surgery: collapse therapy and the removal of primary lesions (Waldhausen et al. 1996; Yan and Duanmu 2003). The aim of the first type is to collapse the lung and chest by removing part of the ribs to change the thoracic shape and promote the cavity closure. The effects of collapse therapy are not stable, because it is an indirect treatment. What's more, postoperative thoracic deformation is particularly noticeable, leading patients to reject this operation and prefer lesion removal instead. Different procedures are used to remove lesions according to their size and the area of the lung affected. The different types of excisions are wedge resection, lung segment resection, lobectomy, composite resection (resection of one or two lobes of the lung and a lung segment, mainly referring to the right middle and right upper lobe resection, or right lower and right middle lobectomy, or right upper and right lower lobe tip resection, or left upper and left lower lobe tip resection), pneumonectomy, and pleural pneumonectomy.

Wedge Resection is suitable for peripheral pulmonary lesions that are very focused, especially when it is difficult to distinguish the lesions from lung cancer. This procedure will be used when doing a biopsy for cancer confirmation, and small resections can be done via minimally invasive thoracoscopic surgery.

Lung Segment Resection or segmentectomy is a normal surgical procedure for TB treatment. It is widely used for resection of the left upper lobe segment, the tongue segment of left upper lobe, or the bilateral lower lobe tip segment. Treatment in surgery for the surface sections should be separated along the lung segment, and, for best results, the segment surface should not be sutured. If there is serious air leakage, a bioglue or surgical sealant can be sprayed at the point of the leak. Segment surfaces must not be handled with the stapler, for sutures make lung resections meaningless. The advantages are less removal of lung tissue, and lower impact on patients' lung function. Unfortunately, there are few patients whose lung lesions are limited to a segment and thus good candidates for lung segment resection.

Lobectomy is, generally speaking, the best procedure in surgical treatment of PTB. It has less effect on a patient's cardiopulmonary function and any complications can be more easily remedied. This procedure is particularly appropriate for patients with cavitary TB, where lesions are mainly focused on the upper lobe. As with wedge and lung segment resections, the procedure is only applicable in a small number of cases as TB is not often confined to one part of the lung. There are often some big lesions around the main lesions, especially in patients with incomplete lung fissures. This can lead to adjacent lung tissue being compromised. For complete clearing of lesions, compound removal is often necessary. For patients with lung lesions limited to one side, pneumonectomy should be adopted for its broader effect.

Pneumonectomy is often used in severe TB, including drug-resistant TB. The surgery removes the entire nonfunctioning lung of one side. In the short run, this not only removes the lesions, but also increases the blood oxygen saturation by cutting off the affected lung which blocked the supply of oxygen to the blood. However, long-term negative consequences cannot be avoided. Twenty years after pneumonectomy, the ligation of lung arteries can cause increased blood flow to the intact lung, which can lead to pulmonary hypertension or pulmonary heart disease.

Generally speaking, surgery for TB is more difficult than surgery for lung cancer. Due to long-term inflammation caused by TB, there are often extensive and closely located pleural adhesions. This can typically cause bleeding when separation is attempted. When parts are closely adhered, extrapleural separation should be used to reduce the bleeding and any damage to the surface of the lung. This can reduce excessive contamination and the need for a blood transfusion. Additionally, TB patients have a greater chance than cancer patients of having the hilar lymph node infected and inflamed by TB. Therefore, the adhesion with the surrounding lymph nodes is sometimes very close, leading to separation difficulty. For these reasons, lung excision surgery of TB patients (especially for MDR-TB patients) requires the use of a thoracoscope, which is difficult in surgery. Currently, thoracotomy is still recommended for TB surgery.

Thoracoscopic surgery has been widely used. It has been the routine treatment for many patients with mild illness (Wang and Yang 2006). However, some patients with more serious illness such as ones with extensive pleural adhesions cannot receive thoracoscopic surgery, due to its restrictions.

14.5.1 Surgical Anesthesia

General anesthesia uses double lumen intubation and one-lung ventilation to prevent the bacteria spread to the contralateral lung, and the classic surgical approach is to open the chest. Going into the chest through the posterior lateral incision in order to expose the chest fully is often used. With the rapid development of surgery in recent years, thoracoscopic lung resection has been widely used, both in China and abroad.

14.5.2 Laboratory Tests for Specimens after Surgery

In order to aid in anti-TB treatment after surgery, tests of resection specimens include not only additional pathological tests, but also routine bacteriological examinations, with some specimens taken for Lowenstein–Jensen culture and drug sensitivity tests. Culture susceptibility results can guide postoperative anti-TB treatment programs to improve their success rate.

14.6 The Complications and Treatment after Surgery

Due to the strict selection of cases, anesthesia technology development, and effective postoperative antituberculous therapy, the postoperative mortality and complication rates of lung resection for PTB patients have gradually decreased. Because general surgery in treatment of PTB in recent years has become a routine operation, specialized reports about its complications are rare. Comparatively, there are more reports on drug-resistant TB operations; the postoperative mortality and complication rates for surgery of drug-resistant PTB are higher than those of lung cancer (Kim et al. 2008; Yu and Fu 2009).

14.6.1 The Postoperative Mortality

In 1970s, before rifampicin was discovered, it was reported that the mortality rate from TB surgery was 2–5 %, and the complications rate was about 10–20 % (Jones 1957). In recent years, with the rapid developments in surgery and anesthesiology,

mortality and complications from general PTB surgery have been significantly reduced, but there is no evidence-based medical statistics report. The data published today mainly focuses on drug-resistant TB, especially MDR-TB.

Mohsen et al. (2007) reviewed 23 surgeries for MDR-TB. Of the 11 patients who underwent pneumonectomies, two developed postoperative empyema; of these, one developed additional complications including a bronchopleural fistula and died in hospital, yielding a mortality rate of 4.3 % (1/23). Yu and Fu (2009) reviewed 133 surgeries for MDR-TB and reported a postoperative mortality of 2.3 % (3/133), with 2 cases dying from postoperative respiratory failure and 1 other case caused by postoperative thoracic aortic rupture. Most of the postoperative deaths reported were pneumonectomy patients. Therefore, pneumonectomy should be taken into careful consideration.

14.6.2 Common Complications and Treatments

Bleeding is the most common complication in the surgical operation for PTB. This is common knowledge, but why is the risk of bleeding so much higher than other general surgical operations? The pleural cavity is under negative pressure, making it more susceptible to bleeding. After lung resection, pressure of the pleural cavity should be negative for patient's breathing. Thus, the surgical wound surface in the pleural cavity is completely exposed to negative pressure, which can turn small-scale intrathoracic bleeding into more significant bleeding or even a huge hemorrhage. Therefore, hemostatic requirements are more stringent in lung surgery than in general surgery.

Bronchopleural fistula (BPF) and empyema are the most difficult complications following PTB surgery, with high incidence and lasting effects on patients (Gu et al. 1964). Patients with endobronchial TB have a significant risk for developing BPF. The resection stump and its anatomical features can inherently create conditions for BPF. Normally, cartilage will support the bronchi, but after resection, the sutured stump will have some tension. Additionally, the optimal condition for surgical wound healing is contact between like tissues. After bronchial resection, the stump cannot contact similar tissue, and this affects healing. As a result, the development of a stump fistula has become one of the most common complications of PTB surgery. In order to solve the problem of postoperative bronchopleural fistula, intraoperative stump embedding after treatment has become an essential step in surgery. The stumps are usually embedded by a pedicled pleural valve, whereas a pedicled muscle flap could be better. From the early twentieth century on, much research has been focused on the bronchial stump suture methods. Xin Yuling, Hu Qibang, and Zhao Zhiwen from Beijing Tuberculosis and Thoracic Tumor Research Institute (now the Beijing Chest Hospital) improved the bronchial stump suture technique after lung resection by removing bronchial stump cartilage and suturing the stump layer to layer (Xin and Ge 1964). It significantly reduced postoperative bronchopleural fistula incidence, but has not been widely used because of its degree

of difficulty. With the development of surgical instruments, fasteners are usually used to treat the stump, but it is not yet known whether fasteners are better than sutures. In Yu and Fu's report of 133 cases of MDR-TB patients (2009), nine developed bronchial stump fistulas postoperatively. BPF was positively correlated with a preoperative sputum positive result, especially preoperative bronchial TB. Wang et al. (2008) reviewed 56 MDR-TB surgeries and also found that endobronchial TB was significantly correlated to the development of BPF. Bronchial stump reinforcement significantly reduced the incidence of BPF.

Fistula of the lung surface often occurs after pneumonectomy. Pulmonary surface damage is inevitable because of the operation trauma. But if it prolongs, it may cause serious complications such as thoracic cavity infection. There is no standard for the postoperative air leaks extent and time, but generally speaking, more than a week is considered abnormal. It can be fixed by glue or some other treatments.

A postoperative residual cavity after pulmonary resection is apparent. All the tissue above and around the chest cavity is bony. Only the diaphragmatic surface is soft. After the lung is resected, the original space is occupied by the remaining lung. The remaining lung cannot inflate to the exact shape as the one removed, so a residual cavity is inevitable. Usually, the stump will disappear completely after half a year, and a longer time is needed for the cavity to recover if one side of the lung has been completely resected.

14.7 Postoperative Treatment and Prognosis

Because PTB is a systemic disease, and surgery cannot completely resect lesions, postoperative antituberculous therapy has become one of the key points for a cure. It is suggested that anti-TB chemotherapy should continue for 1 year after surgery, especially for the patients who cannot be excluded from lung cancer. If performing surgery directly without preoperative chemotherapy, postoperative antituberculous therapy should always continue for at least 1 year. Postoperative chemotherapy recommendations range from a minimum of 6 months to a maximum of 84 months, with the longer treatment times suggested for patients with MDR-TB (Tang and Xiao 2003; Takeda et al. 2005; Mohsen et al. 2007; Shiraishi et al. 2009; Yu and Fu 2009). Specific antituberculous programs can refer to what was administered before surgery or can be implemented according to the bacterial culture and drug sensitivity results of the specimens obtained from the operation. Generally speaking, if regular postoperative anti-TB drug therapy is implemented, PTB patients, including MDR-TB patients, can gain satisfactory prognosis with surgical treatment.

In the last 10 years, with the increased number of MDR-TB patients, the number of patients who require surgery has also increased. However, it must be emphasized that surgery is not the final treatment for PTB, especially for the MDR-TB patients. The factors for an effective surgery include the properly indicated patients, patients' understanding and cooperation, adequate preoperative preparation, proper operation time, an experienced operation team, and regular postoperative treatment.

Surgical treatment of TB can not only effectively reduce the patient's suffering, but it can also effectively eliminate an infectious source. Surgery is an indispensable method in the TB control process.

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Chapter 15
Diagnosis and Interventional Therapy by Bronchoscopy

Yu Fu and Weimin Ding

15.1 The History of Bronchoscopy

Bronchoscopy was first applied in general practice by Gustav Killian in 1897. At that time, the bronchoscope was a rigid tube made of copper and could not bend. When patients underwent a rigid bronchoscopy, they had to keep a straight line from the mouth to the airway. As a result, the patient had to lean his head back at a large angle, causing great pain during the examination. What's more, those patients who could not tilt their heads backward enough, such as cervical spondylosis patients, were unable to undergo bronchoscopy.

In 1966, Shigeto Ikeda invented the flexible bronchofiberscope (BFS) and, by the end of the decade, used it in general practice. Compared to the rigid bronchoscopy, BFS has the advantages of being flexible, easy to operate, and having a small outer diameter. It also expanded the range of observation. Rigid bronchoscopy could only observe the lobe opening, but BFS could observe the opening of a subsegment or even a thinner bronchus. The use of glass fiber increased the light available for examination. Meanwhile, BFS didn't require patients to hold an unnatural position and thus decreased patient discomfort. The use of BFS made bronchoscopy more popular.

Along with the rapid development of digital imaging technology, flexible video bronchoscopes came out in the 1980s, marking an essential change for the operation

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and imaging system of bronchoscopy. Video bronchoscopes are easy to operate and provide clearer imaging. Flexible bronchoscopy (including BFS and video bronchoscope) is widely used for clinical diagnosis (Becker 2010).

Though the earliest bronchial interventional treatment can be traced back to Killian's use of a rigid bronchoscope to remove foreign matter from the bronchus, intervention reached a new level in the early 1990s when laser technology was applied to the trachea and bronchial lumen (Becker 2010). As flexible bronchoscopy and related technology develop rapidly, the applications for its use in intervention therapy continue to expand. Interventional therapies include drug delivery, sputum aspiration, fistula block, thermal ablation, cryotherapy, stent, expansion, and so on (Simon and Simon 2009).

In view of the characteristics of rigid bronchoscopy, it was not the first choice for tuberculosis (TB) diagnosis and interventional therapy in general practice. It was mainly used for removing large-scale foreign matter from the airway and the interventional treatment of tumors within the airway. Flexible bronchoscopy, however, provides the opportunity for extensive intervention therapy of TB.

15.2 Indications and Contraindications for Flexible Bronchoscopy in TB Patients

This section describes the essential considerations for clinicians to determine if a flexible bronchoscopy examination would be suitable for a patient.

15.2.1 Indications

Flexible bronchoscopy may be used for a preoperative routine examination for patients who are prepared to undergo lung surgery. Flexible bronchoscopy may be indicated by the following conditions, assuming the patient agrees to the procedure and has been informed of possible complications (Gasparini 2011):

- Long-term cough or cough consistent with lung lesions.
- After anti-TB treatment, there is obvious absorption as seen in patient's chest radiograph, but no obvious improvement in the patient's cough.
- The chest X-ray or CT scan confirms that there are space-occupying lesions in the bronchial lumen (or a suspicion).
- The chest X-ray or CT scan confirms that there are space-occupying lesions or diffuse lesions in the lung, or the presence of symptoms such as atelectasis, or hilus pulmonis or mediastinum lymphadenectasis.
- Haemoptysis or limited stridor.

15.2.2 Contraindications

- Patients with severe cardiac insufficiency, and who have had myocardial infarction within a month. For people with heart diseases, such as serious arrhythmia, unstable angina, or ventricular aneurysm, indications should be strictly monitored.
- Patients who have had massive hemoptysis within a week.
- Patients with abnormal bleeding tendency, amounts of platelet, or coagulation function.
- Pulmonary arterial hypertension patients with seriously low oxygen or respiratory failure, severe hypertension patients who failed to control their blood pressure. Patients with serious abnormal liver and kidney function should be cautious when they are going to receive bronchoscopy.
- Patient has an extremely weak constitution and is not likely to tolerate the procedure.
- Patient refuses bronchoscopy.

15.3 Flexible Bronchoscopy Operation Procedures

Once a flexible bronchoscopy examination is chosen, there are four phases of the procedure: preparation, administration of anesthesia, the bronchoscopy itself, and post-procedure care. There are important considerations in all phases to ensure an optimum operational result (Prakash 1999).

15.3.1 Preparation

Prior to bronchoscopy, the patient's medical history should be discussed, especially whether there is a history of abnormal bleeding or an allergy to tetracaine, lidocaine, or other drugs used in the procedure. Routine examinations include blood tests, coagulation function, HBV antigens and antibodies, HCV, HIV antibody, syphilis, and so on. For the older patients or those who have poor lung function, an electrocardiogram is necessary. Asthma patients are advised to use bronchodilators before bronchoscopy. Patients should fast 4 h before the procedure, and drinking water is forbidden 2 h prior to the procedure. Patients who are critically ill should have intravenous access (Zuccatosta 2011).

15.3.2 Anesthesia

Generally, 10 min before bronchoscopy, an intramuscular injection of 5–10 mg midazolam is given. Currently, the application of atropine is controversial. An intramuscular injection of 0.3 mg atropine 10 min prior to bronchoscopy has been used

to reduce tracheal and bronchial secretions and bronchial spasms, making inspection easy. Most experts do not advocate the general application of atropine, however, mainly because there is no significant difference whether the patient uses it or not. Application of atropine gives patients xerostomia for a long time after use, and as the examination prohibits drinking water for 2 h after inspection, patients may become very uncomfortable. Atropine is used only when the patient has quite a large amount of secretion or is receiving interventional bronchoscopy therapy rather than in a simple inspection.

For preliminary anesthesia, aerosol inhalation of 3–5 mL of 1 % tetracaine (or 3–5 mL of 2 % lidocaine) allows droplets of anesthetic to reach the pharynx, larynx, trachea, and bronchi. After that, 1 % tetracaine (or 2 % lidocaine) is sprayed on the palatopharyngeal arch, uvula, tongue center, retropharynx, and epiglottis to supply aerosol inhalation. Generally, each part is sprayed twice, and then the spraying is repeated. The nostril will also be sprayed with anesthesia if the scope is inserted through the nasal cavity. The final anesthesia could be added by thyrocricocentesis, ear–nose–throat special injector, or bronchoscopy after it goes into the trachea. The only anesthetic suggested for this step is 2 % lidocaine, because in the past, many patients died from excessive tetracaine use. Considering that the anesthetic effect of lidocaine is also good and its maximal dose is much higher, the anesthetic used in the trachea has changed to lidocaine. The general amount is 5–8 mL but it can be added several times if needed. In the past, only the severe patient in good spirits could receive bronchoscopy under general anesthesia. But in recent years, “painless bronchoscopy” has become more popular. While general anesthesia is only used for extreme cases, intravenous delivered anesthetic, such as propofol and fentanyl, can also be used. It should be emphasized that any patient administered a sedative or general anesthetic shall be managed and monitored according to the requirements of anesthesiology while anesthetized and cannot leave or be discharged before regaining consciousness (Jantz 2009; Sarkiss 2011).

15.3.3 Bronchoscopy

The supine position is the most common position for bronchoscopy. This position is comfortable for both patients and operators, and is convenient for handling in the event of an accident. The sitting position can also be adopted, which may reduce patient nervousness, but is not so convenient in the event of an accident. No matter what position is chosen, the bronchoscope should be sent to the trachea and bronchus from the mouth during inspection, and for special inspection, it can be sent from the nasal cavity. It is necessary to be prepared for cardiopulmonary resuscitation (CPR), and oxyhemoglobin saturation should be monitored during inspection. Visual inspection, tissue biopsy, and/or bronchial/bronchoalveolar lavage can be performed (see Sect. 15.4.2).

15.3.4 Post Bronchoscopy

Patients should be told not to eat and drink 2 h after bronchoscopy. Patients should be closely observed whether there are any complications such as massive hemoptysis, and deal with them positively.

15.4 Diagnosis of Bronchial Tuberculosis (BTB) via Bronchoscopy

Theoretically, lesions in any part of the lung can be observed generally by flectional bronchoscopy. For the lesions of the upper segments of the trachea and bronchus, preliminary diagnosis can be made through direct observation of bronchoscopy images. According to the direction of the lumen, any tortuosity of the airway can be known. Thickness of the lumen can reveal whether it has suffered external pressure and had stenosis. Visual inspection can reveal whether there is pressure in the bifurcate parts of the entire bronchus, if there is luster on the tracheal and bronchial mucosa, and whether there are symptoms such as congestion, edema, erosion, ulceration, thickening, and scarring. Bronchoscopy will show any necrosis on the surface, any neoplasm in visual range, and any obvious hyperemia on the surface of the neoplasm. Whether the fundus is infiltrated can be determined, and, if so, to what extent, and whether the tissue is brittle and easily hemorrhagic. The color and quantity of the lumen secretions can be seen, and, if they are hemorrhagic, the location of the hemorrhage and whether it is a blood streak, bloody sputum, or from whole blood (Chinese Thoracic Society 2002).

There is no standard for BTB classification though experts have proposed standards ranging from four to nine types of BTB (Kashyap et al. 2003; Rikimaru 2004a, b). Chinese experts have considered histopathological features, outcomes of BTB, and literature about BTB, to propose a "five types" standard, which is more meaningful for BTB treatment protocols and outcome prediction (Editorial Board of Chinese Journal of Tuberculosis and Respiratory Diseases 2009). These five types are described below.

Type 1: inflammatory infiltrative BTB is characterized by tracheal and bronchial mucosa hyperemia and edema and exhibits some off-white miliary nodules on local lesion mucosal surfaces. The airway lumen manifests varying degrees of stenosis due to mucosa and mucosal tissue swelling (Fig. 15.1). In this stage, an acid-fast bacilli test from the brush biopsy of bronchial mucosal lesions will have a high bacteria positive rate. It is consistent with early histological changes of TB lesions.

Type 2: ulcerous necrotic BTB lesion areas are characterized not only by hyperemia and edema, but also by jagged ulcers covered by off-white caseous necrotic tissues. The ulcer's depth differs according to the degree of the lesion. For some patients, it only appears on the surface of mucosa. In more severe cases, the depth can be embedded to the bottom of the mucosa. In addition, the ulcer can lead to

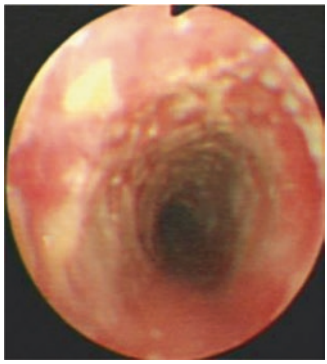

Fig. 15.1 Type 1: inflammatory infiltrative BTB

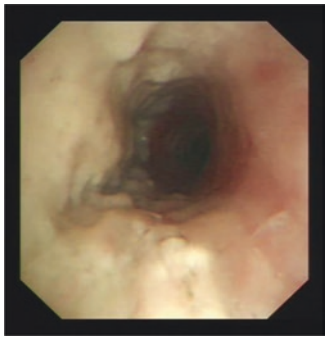

Fig. 15.2 Type 2: ulcerous necrotic BTB

tracheal and bronchial cartilage damage, and the lesion area can bleed easily if touched. This is characteristic of the period when the TB lesion is apparently manifested (Fig. 15.2). In this period, the relevant ratio of acid-fast bacilli is also high. Bronchial fistula induced BTB, caused by lymph node TB, often manifests as this type.

Type 3: granulomatous hyperplastic BTB occurs when the hyperemia and edema of tracheal and bronchial mucosa have mitigated, mucosal ulcer begins to repair, and hyperplastic granulation tissue can be seen in the visible lesion area and can partly block the lumen (Fig. 15.3). This is characteristic of the transitory stage from TB damage to repair. Typical multinucleated giant cells and Langerhans cells can often be seen in the biopsy.

Type 4: scar stricture BTB is referred to as the healed phase of TB. Normal tracheal and bronchial mucosal tissue is replaced by hyperplastic scar and fibrous tissue. The lesion involves the bronchus, often with stenosis or even blockage by hyperplastic scar tissue and its contracture (Fig. 15.4). The tuberculous effusion is usually stable or recovered. Brush biopsy smear for acid-fast bacilli often shows a negative result, and the biopsy usually does not reflect abnormal situations.

Type 5: bronchomalacia involves lesions with the disappearance or rupture of the tracheal and bronchial cartilaginous ring. Due to the collapse of the trachea and bronchus, the lumen is blocked to varying degrees. This is quite obvious when intra-

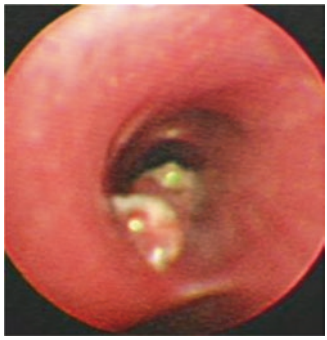

Fig. 15.3 Type 3: granulomatous hyperplastic BTB

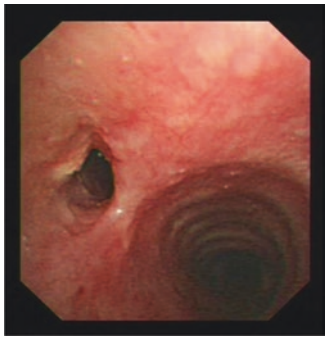

Fig. 15.4 Type 4: scar stricture BTB

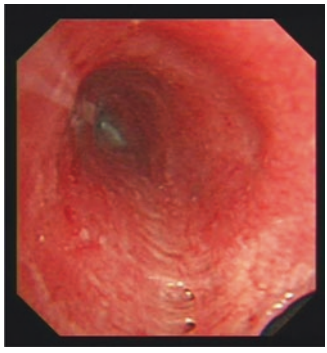

Fig. 15.5 Type 5: bronchomalacia

pleural pressure increases during expiration or cough, and when the bronchus located far from lesions appears with varying degrees of bronchiectasis (Fig. 15.5). When the patient is confirmed with this type, his tuberculous effusion is often stable or recovered.

Besides the common findings in BTB using the bronchoscope, some visible changes are valuable for diagnosis of past infection. For example, if there are black spots or powder deposited in the trachea and bronchus, especially many black spots deposited in the crotch of the patient's trachea and bronchus, it is likely that the

patient has suffered from BTB or mediastinal TB. In addition, some BTB patients will show a scar or tortuosity in their bronchus after BTB has healed. Once these changes appear, it is also likely that patients have suffered from BTB.

15.4.1 Epidemiology of BTB

Bronchial TB is a common type of TB. Literature outside China reported that about 10–40 % of active TB patients have BTB (Kashyap et al. 2003; Rikimaru 2004a, b). At present, there is no epidemiological survey for BTB in China. According to the bronchoscopy observation of 1992 cases of TB patients in the progressive stage, Zhang (2008) found that 1198 cases were from single TB, and the other 794 involved combined pulmonary and bronchial TB (39.86 %).

Only bronchoscopy can definitively diagnose BTB. Primary diagnosis can be made with visual inspection using bronchoscopy. However, due to the ever-changing manifestations of BTB and the features of some diseases similar to BTB, there are errors in diagnosis when relying solely on the naked eye. This is why bacteriological or pathological diagnosis has become the gold standard. Confirming diagnosis of BTB relies on both bronchoscopy and bacteriological or pathological results (Ding and Fu 2011).

15.4.2 Common Inspection Methods

In addition to visual observation, physical specimens from biopsy, brushing, and/or lavage (described below) can be checked for any pathology, bacteriological properties, etc. For the lesions in the distal side of the lung, distal lung biopsy can be used. Lavage or blind brushing can be used in the lung lobe or opening of the pulmonary segment that corresponds to the lesions. Also, biopsy, brushing, and other inspections can be adopted for the peripheral lesions under the videofluoroscopic swallowing study (VFSS). Moreover, after bronchoscopy, the positive rate of the sputum reserved for bacteriological or cytological inspections will increase 10–20 % due to the bronchoscopy's strong stimulation of the bronchus.

Biopsy is done to confirm BTB. Hyperplasia, ulcer, and erosion of granulation tissue are often seen in the bronchial lumen. BTB is mainly observed as granulation tissue hyperplasia with lots of caseous necrosis on the surface of granulation. Part of the necrosis should be tweezed in inspection, and a local biopsy can be done after the granulation tissue has been exposed. This increases the rate of positive diagnosis. The specimen should be immediately put into a 10 % formalin solution. Acid-fast stain should be done for confirmation, because pathological changes of TB are similar to the histological features of other inflammatory granulation diseases.

Brushing is the most common diagnostic method for BTB. The advantage of this method is that it is simple, fast, and has a high accuracy. It is especially convenient

for diagnosis of ulcer and erosion types. In order to decrease contamination and increase the positive rate, use a disposable brush (preferably one with a sheath). After bronchoscopy, the sputum smear positive rate can improve.

Lavage can be classified as bronchial lavage (BL, also known as bronchial washing) or bronchoalveolar lavage (BAL). The distinction between the two lies in the different methods of anesthesia and dosages of normal saline used.

Concrete operations are described as follows (Chinese Thoracic Society 2002):

- For BAL, apply local anesthetic by injecting 1–2 mL of 2 % lidocaine into the pulmonary segment needing lavage through a thin silicone tube in the biopsy hole. This step can be omitted in bronchial lavage.
- Wedge the top of a bronchoscope closely into the opening of the pulmonary segment or subsegment, and quickly inject 37 °C sterile saline through the silicone tube via the biopsy hole. For BAL, inject 25–50 mL at a time, with a total volume of 100–250 mL (generally no more than 300 mL). When doing bronchial lavage, generally inject 10–20 mL each time, and repeat once.
- Immediately suck the lavage fluid with 50–100 mmHg (1 mmHg = 0.133 kPa) negative pressure. Generally the recovery rate of lavage fluid is 40–60 %.
- Submit lavage fluid for diagnosis.

Acid-fast bacilli can be found directly in the BL/BAL fluid. At present, lavage is an effective method that can yield more sputum directly. This is especially useful for diagnosing DR-TB patients whose sputum culture is negative, as they cannot be easily diagnosed in order to begin effective treatment. Note that if the sputum used for culture is collected after bronchoscopy, lidocaine in the bronchial secretions may reduce positive results. Conventional acid-fast bacilli culture and drug sensitivity experiments for bronchoscopy patients can help to find drug-resistant patients early.

Transbronchial needle aspiration (TBNA) uses a thin biopsy needle penetrating the trachea and bronchi wall in order to obtain a pathology sample. This method has an advantage for accuracy, safety, and cost by means of the fine needle aspiration biopsy. It suits the qualitative detection of mediastinal and pulmonary hilum lymphadenectasis. Bronchoscopy, chest CT imaging, and Wang's location method are used to set the point of puncture. The puncture needle is inserted into the lymph node across the airway wall to collect the specimen by the syringe that is connected with negative pressure. Then the specimen is smeared for further pathological examination. After the puncture, the surface of the puncture site is brushed and can increase the positive rate of detection. There are a few complications for TBNA, mainly bleeding in the punctured area, which can be stopped after treatment. Complications such as pneumothorax and pneumomediastinum are occasionally reported.

Currently, Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is gradually replacing TBNA (Medford et al. 2010). Ultrasonic testing with bronchoscopy could localize the lymph node around the airway more precisely. Additionally, there is a certain angle between the needle and the direction of the airway. That's why EBUS-TBNA will become more secure, accurate, and

convenient. At present, it is mainly used for the differential diagnosis of lung cancer, lymphoma, and sarcoidosis. Symptoms of enlarged mediastinal lymph nodes and mediastinal lymph node TB that has not festered can be diagnostic too.

15.4.3 Bronchoscopy Complications

Though bronchoscopy is commonly performed, there are still safety considerations for this procedure. Patients should be monitored for potential complications including bleeding, allergic reaction to the anesthesia, laryngeal spasm, hypertensive crisis, low blood sugar, panic attack, or other unforeseen circumstances (Facciolongo et al. 2009).

Bleeding is the most common complication during bronchoscopy. When bleeding is excessive or the trauma is relatively large, the patient should be told to minimize coughing as much as possible after the examination. The patient should be held for 20 min of observation and should not be discharged until the bleeding has stopped. In general cases, no treatment is needed for a small amount of bleeding during the inspection. If the patient bled much during the inspection, a small amount of vasoconstrictor drugs such as the adrenal solution (1:10,000) can be used locally to stop bleeding. After the biopsy or brush biopsy, some patients (usually a cancer patient or the rare TB patient) will suffer hemorrhage caused by large ruptured blood vessels. When there is heavy bleeding, removal of the blood before clotting is the first and most important task, because the blood clot can block the respiratory tract and suffocate the patient. Try to ensure the patient stays calm. In order to reduce stimulation, bronchoscopy should be directed away from the bleeding point. At the same time, a 1:10,000 solution of epinephrine can be injected from the biopsy hole to the bleeding site via bronchoscope. An injection of 2–5 mL can be applied repeatedly. In principle, local hemostatic agents such as thrombin are forbidden, because blood coagulation drugs can cause blood to clot rapidly in the bronchus. Once blood is clotted, it is very difficult to suck out by bronchoscopy. A blood clot can lodge in the airway and impede the respiratory tract, or even completely block the airway, causing suffocation. The patient should assume a side-lying position, with the bleeding side down to minimize bleeding side effects on the non-bleeding side of the respiratory tract. After the general treatment above, if the bleeding has stopped, bronchoscopy can be dropped out or withdrawn once the patient is observed for 5 min without any obvious bleeding. If the bleeding continues, an anesthesiologist should be invited for consultation while the active treatment is being done, and an endobronchial intubation double-laparoscope should be prepared to ensure an open airway if necessary. Ensure that patient's venous access is clear. Hemostatic drugs such as posterior pituitary hormone and blood clotting enzymes can be offered through the venous access. If the patient bleeds excessively, normal saline and a plasma substitute can be administered via IV and oxygen saturation and vital signs should be monitored. In order to strengthen local hemostasis, other methods to stop the bleeding points, such as argon beam coagulation, can be used. An air bag or membrane attached stents can be applied for local hemostasis. To the stable patients

with out of control bleeding, bronchial artery embolization or, in an emergency, surgical removal can be considered.

Allergic reaction to tetracaine, lidocaine, and other anesthetics is uncommon, but is seen occasionally. Once the patient is allergic to a specific drug, anti-allergy treatment should be given immediately, and anti-shock treatment should be given to the patient in shock.

Laryngeal spasm may be induced by improper technique, an insufficient amount of narcotic drugs, drug allergies, or other reasons. Once laryngeal spasms happen, the patient will feel suffocated with the symptom of a high-pitched sound of wheezing. If the bronchoscope is still in the trachea of the patient, the doctor must be calm at this time, under the premise that bronchoscope is well protected, and not pull out the bronchoscope. Oxygen should be supplied and drugs that induce spasmolysis can be delivered by biopsy hole. If the bronchoscope has been removed from the trachea, the largest available syringe needle should be immediately used to pierce the trachea to keep the respiratory tract open. Other rescue measures should be performed as needed.

Hypertensive crisis occurs mainly due to fasting, water deprivation before examination, not taking antihypertensive drugs on the day of the procedure, coupled with the fear of a rough and lengthy operation. The unforeseen situation such as intracranial hemorrhage can even happen. First, the examining physician should think about the possibility of hypertension, which could be confirmed just by checking the blood pressure. If there is a hypertensive crisis, the bronchoscopy operation should stop immediately. If only high blood pressure appears without abnormal symptoms of consciousness, antihypertensive treatment can be used. If the patient has abnormal changes such as coma, both sides of the body movement being abnormal and bilateral pupil constriction, emergency treatments such as lowering blood pressure, dehydration, lowering the intracranial hypertension and supplying oxygen should be immediately given. For the rare patient who develops intracranial hemorrhage, emergency lifesaving treatment should be performed; intracranial hematomas should be removed as soon as possible to avoid any sequelae.

Hypoglycemia is also common, especially for the elderly. Because of the fasting and water deprivation, the chance of hypoglycemia is relatively high, especially there is long wait before the examination. In order to prevent this complication, diabetic patients should be checked as early as possible. Generally speaking, hypoglycemia is not too harmful for nondiabetic patients and glucose should only be supplied in serious cases.

15.5 Flexible Bronchoscopy for Interventional Treatment of BTB

In addition to diagnostic procedures, flexible bronchoscopy can also be used to deliver interventional BTB therapy. These treatments include localized drug delivery, cryotherapy, stent placement, and balloon dilation; the varying effectiveness of these methods in clinical practice is discussed below.

15.5.1 Drug Delivery by Bronchoscopy

For the patients with confirmed BTB, drugs can be delivered by bronchoscopy in addition to systemic anti-TB treatment (Ding et al. 2010b). This can be particularly effective for patients with inflammatory infiltrative, ulcerous necrotic, or granulomatous hyperplastic types of BTB. Administration of drugs locally can increase drug concentration in local lesions, strengthen the role of bactericidal antimicrobials, and reduce systemic adverse drug reactions. It can also promote the absorption of local inflammation and speed up the recovery of bronchial mucosal congestion and edema, and thus reduce the possibility of bronchial stenosis. The specific steps are to clean up the sphacelus by bronchoscopy as much as possible and then inject anti-TB drugs into the granulation tissue. Generally, doses of 0.1 g isoniazid, 0.45 g rifampicin, and 0.2 g kanamycin or 0.1 g amikacin can be injected at the same time, 1–2 times a week. As the injected drugs are liquid, they cannot stay in the bronchus long, which limits the treatment effect. In order to solve this problem, Chen et al. (2008) reported that carbomer gel can be added in the anti-TB drugs to prolong the drug exposure time.

15.5.2 Thermal Treatments for BTB

Thermal treatments such as laser, hyfrecator, microwave, and argon plasma coagulation are all widely used in the treatment of tumors (Mehrishi et al. 2001; Bolliger et al. 2006; Wahidi et al. 2007). In the case of BTB, however, these treatments can rapidly make the diseased tissue solidified, dried, and necrotic. In the recovery process, the proliferation of connective tissue and formation of cicatricial contractions can lead to bronchial restenosis. Given these long-term effects of heat treatments, Chinese experts now avoid the use of heat treatments except in very special cases (Editorial Board of Chinese Journal of Tuberculosis and Respiratory Diseases 2009).

15.5.3 Cryotherapy

In 1983, based on animal experiments, Rodgers successfully used endoscopic cryotherapy to treat benign stenosis of the trachea and main bronchus for the first time (Huang 1991). In 1994, Petrou and Goldstraw also achieved good results using the same method. Another study suggests that bronchoscopic cryotherapy has a low risk of perforation (Schumann et al. 2010). As cryotherapy has both short-term and long-term benefits, it is very suitable for the treatment of BTB. For the tracheal and bronchial granulation tissue, cryotherapy is also applicable. Generally, the treatment is 1–2 times per week, and 3–5 min each time. Cryotherapy requires about a

4–6 week course of treatment to effectively cure stenosis. This leads to better recovery of the bronchial mucosa, with less scarring and a reduced incidence of bronchostenosis in the long run (Mu et al. 2011).

15.5.4 Stent Treatment

As a result of stent treatment in other visceral organs, bronchoscopic stent treatment developed in the 1990s (Ranu and Madden 2009; Lee et al. 2010; Flandes Aldeyturriaga et al. 2010). Significant practical experience has been gained with bronchoscopic stent treatment, especially in the treatment of cancer. But it is controversial for the treatment of benign lesions in air passages, especially for BTB (FDA 2005). The supporters believed that the effect was good, but the objectors argued that in the long term, the following issues should be resolved:

- Metal fatigue after long-term placement may occur. Once the stent is placed, it cannot be taken out within 3 months, and removal is difficult. Most BTB patients are young, which means that stents may be placed in the patient over several decades. There are concerns for metal fatigue over such a long time.
- After inserting the stent, both ends of the stent will rub when the patient coughs, increasing the risk for granulomas at both ends and causing air passage restenosis.
- A mesh shaped stent may stimulate the formation of granulation along the mesh.
- Long-term stimulation of the air passage may lead to cancer.

Taking into consideration the problems mentioned above, the clinical practice of stent insertion in the treatment of BTB is not popular. Chinese experts agree that stents should not be used in the treatment of BTB unless there is bronchial softening or alveolar sac expansion failure. Recently, more reports show satisfactory results for stents in the treatment of BTB (Han et al. 2005; Ryu et al. 2006; Kim et al. 2007b). It needs to be stressed that it is important to choose the appropriate time for stent insertion. It should be done after the BTB has been controlled. Stent failure rates will significantly increase if inflammation is still present.

15.5.5 Balloon Dilation

In 1991, Nakamura et al. initially reported that fiber-optic bronchoscopy was successfully used in balloon dilation treatment for patients with tuberculate bronchial stenosis. After the reduction of bronchial mucosa inflammation, balloon dilation treatment can be used for TB patients when there is bronchial stenosis left in the upper segment of the bronchus. The theory of bronchoscopy balloon dilation is similar to other expanding treatments. The balloon is placed in the narrow part of the bronchus, and the pressure of the expanding balloon dilates the tracheal and

bronchial lumen (Chung et al. 1991; Low et al. 2004). In theory, the contraction direction of the scars formed by the union of lengthwise lacerations along the bronchus is also along the long axis direction of the trachea and bronchus; therefore, tracheal and bronchial stenosis will not form again. In practice, many have reported clinical success using balloon dilation to treat BTB and airway stenosis (Duan and Fu 2007; Kwon et al. 2009; Ding et al. 2010a).

15.5.5.1 Indications

Balloon dilation can be considered when the patient has achieved regular and effective anti-TB chemotherapy, and cicatricial stenosis appears in the tracheal or bronchial lumen, making the lumen half narrowed or less, with ostiole ≥2 mm; there isn't obvious active BTB in the stenosis, and/or there is bronchial stenosis caused by non-tracheal softening.

15.5.5.2 Contraindications

Balloon dilation is not recommended if the patient's BTB is still active or there is significant inflammation in the bronchus. After bronchiectasis, the damaged mucosa is very prone to new infection, which will seriously influence the effects of the treatment. Balloon dilation is not useful when there is serious damage of lung tissue distant from the stenotic bronchus or there has been obvious bronchiectasis. In this case, even if the stenotic bronchus is expanded, distal lung tissue function cannot be restored, making the bronchoscopy balloon dilation therapy meaningless. This treatment cannot be performed if the bronchial orifice has been completely closed due to the difficulty of inserting the balloon.

15.5.5.3 Expansion Therapy Method

1. The size of the balloon required is dictated by the specific site and the length of the stenosis, so the patient should have a chest CT and 3D imaging of the bronchial stenosis before the operation.
2. General or localized anesthesia is used. If general anesthesia is adopted, do the steps according to the general anesthesia measures; if using localized anesthesia, in addition to the bronchoscopy anesthesia method, add a basal anesthesia such as an intramuscular injection of 5 mg midazolam.
3. When the bronchoscope reaches above the site of the stenosis, the narrow conditions need to be confirmed by gently using pliers under the trachea microscope to explore whether the narrow area can allow the balloon to pass through. If it is concluded from the image that it might pass but it is later found not to pass, cryotherapy can be used to get through the lumen (assuming no major blood ves-

sels are surrounding the stenosis), ultimately allowing for the insertion of the balloon.

4. After the balloon gets through the narrow parts, normal saline can be injected into it to increase the pressure and achieve the purpose of expansion. Generally, the pressure is 3 atm in the beginning and can be gradually increased as needed. The maximum pressure used depends on the highest pressure tolerated by the balloon. The duration of treatment is generally about 1 min, and each operation can be repeated 2–3 times. According to the patient's condition, it can be repeated once again in the next week. Generally, 80 % of the patients can get very good therapeutic effect after 1–3 weeks treatment.

15.5.5.4 Complications

The most common complications are bleeding, bronchial lumen rupture, and bronchial restenosis or redeveloping atresia. Bleeding is the most common complication of all the traumatic treatments. Hemorrhaging from expansion treatment is generally not significant, but can become a factor if the scar is fresh or there is a narrow site near peripheral bronchia. Massive hemorrhage is rare. Tracheal or bronchial rupture is also a complication of expansion treatment. If this happens, mediastinal emphysema and subcutaneous emphysema can also develop (Kim et al. 2006, 2007a).

15.6 Summary

In the absence of specific clinical manifestations and imaging scans, bronchoscopy allows the clinician to diagnose tracheobronchial TB by visual inspection. Flexible bronchoscopy also allows clinicians to obtain specimens via brush, bronchial biopsy, bronchial or bronchoalveolar lavage, transbronchial lung biopsy, or needle aspiration.

Improved flexible bronchoscopy developments combined with other medical advances has opened up a new clinical path for the treatment of TB. Technologies from localized drug delivery, balloon dilation, and stent placement, to laser therapy, argon plasma coagulation, and cryotherapy, offer tools in addition to chemotherapy for the treatment of TB and especially tracheobronchial TB. These interventional therapies may strengthen the effect of anti-TB treatment and can shorten the course of TB control and shorten the course of disease. These interventional therapies may also offer an alternative to more extensive surgical treatments or options for special cases, stenosis, etc. It is conceivable that with the increasing awareness of the interventional utilities of the bronchoscopic technologies, bronchoscopy will play an important role in clinical diagnosis and treatment of TB.

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Chapter 16
Intensive Care Treatment of Critical Tuberculosis

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16.1 Introduction

Despite recent advancements in tuberculosis (TB) treatment, 1–3 % of patients progress to critical TB, which has a high rate of mortality (Agarwal et al. 1977; Frame et al. 1987; Levy et al. 1987). In critical TB, the biological functions of heart, lungs, brain, liver, kidneys, gastrointestinal tract, and other major organs are damaged and cannot maintain proper electrolyte balance. Because critical TB patients are usually highly infectious, the intensive care and support they need must be provided in isolation, away from the general hospital population and from the other critically ill patients. Therefore, specialized TB intensive care units (TBICUs) should be set up in high incidence areas. Sufficient medical personnel and equipment should be provided to ensure treatment.

16.2 Candidates for TB Intensive Care Unit Treatment

Critical TB includes severe pulmonary TB, tuberculous meningitis, severe abdominal TB, tuberculous pericarditis, and severe osteoarthrosis TB. Severe pulmonary TB is defined as more than three lung lesions, the formation of cavities and/or regular emission of tubercle bacillus, as well as serious constitutional symptoms (loss of

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appetite, weight loss, fever, night sweats, and fatigue) with complications such as severe pneumonia and respiratory failure (Zhang 2004). Severe tuberculous meningitis patients have more than two of the following characteristics: disturbance of consciousness (drowsiness, lethargy, and/or coma); serious systemic TB symptoms and/or a temperature above 39 °C for 3 days; protein content progressively increases in the cerebrospinal fluid or is greater than 2100 mg/L; imaging indicates hydrocephalus; presence of cranial nerve palsy, paralysis, or other complications (Wang et al. 2006). Abdominal TB could cause intestinal obstruction, intestinal perforation, and tuberculous pericarditis with pericardial tamponade symptoms. Spinal TB with paraplegia indicates severe osteoarthrosis TB.

16.2.1 TBICU Admission Criteria

As a general rule, the decision to treat TB patients in TBICU should be based on the following criteria: failure of one or more organs; hemodynamic instability; and requirement of endotracheal intubation, mechanical ventilation, or other invasive medical procedures for monitoring (Nava et al. 1998; Task Force of the American College of Critical Care Medicine Society of Critical Care Medicine 1999; Webb 1999; Cai 2006).

Common serious complications in critical TB patients requiring care in the TBICU are as following:

- Acute respiratory failure (requiring mechanical ventilation)
- Possible suffocation in patients with active massive hemoptysis
- Refractory or life-threatening tension pneumothorax
- Severe lung infection
- Multiple organ dysfunction syndrome (MODS)
- Shock due to various causes
- Right-sided heart dysfunction caused by acute pulmonary vascular disease
- Heart, lung, brain, and kidney function need to be closely monitored after surgery
- Severe water, electrolyte, or acid–base imbalance; malnutrition
- Intracranial hypertension and hernia caused by severe tuberculous meningitis

Patients in a terminal state of illness or having irreversible disease are generally not treated in the TBICU.

16.2.2 Critical TB Patients in the TBICU

Respiratory failure is a serious complication which first appeared in critical TB-associated multiple organ dysfunction syndrome (MODS). It is also the main reason to be treated in ICU (Erbes et al. 2006; Silva et al. 2010). Secondary pulmonary infection is the primary cause of increased respiratory failure in cases of

critical TB, followed by hemoptysis and pneumothorax (Rao et al. 1998; Zahar et al. 2001; Lee et al. 2003; Ryu et al. 2007). Respiratory failure can occur for many reasons, including impaired lung function due to lung lesions as well as respiratory muscle fatigue caused by long-term malnutrition and protein degradation, which leads to decreased reactivity to anoxia, carbon dioxide retention, and pump failure (Shneerson 2004; Zhang 2004). The inhospital mortality of respiratory failure caused by pulmonary TB is as high as 69 % (Agarwal et al. 1977; Frame et al. 1987) and is twice that of respiratory failure caused by pneumonia (Levy et al. 1987; Confalonieri et al. 1999; Jolliet et al. 2001).

From a clinical viewpoint, TB is a chronic wasting disease. More than 90 % of critical TB patients suffer anemia, in which more than half have hemoglobin levels <9 g/dL. About 67.2 % of severe TB patients also suffer hypoproteinemia (Erbes et al. 2006). At the same time, an impaired immune system leaves patients vulnerable to secondary pulmonary infection or sepsis. In response to sepsis, the effector cells release inflammatory mediators uncontrollably, which leads to MODS. Multiple studies have shown that 30–90 % of TB patients in the intensive care units suffer sepsis, while the incidence of MODS ranges from 19 % to as high as 80 % (Zahar et al. 2001; Lee et al. 2003; Erbes et al. 2006; Ryu et al. 2007; Chen and Zhu 2010; Silva et al. 2010). Domestic and international research has shown that sepsis and MODS are independent factors which affect the mortality of hospitalized critical TB patients (Lee et al. 2003; Erbes et al. 2006; Ryu et al. 2007; Chen and Zhu 2010).

16.2.3 APACHE II Scoring System for TB Patients with Respiratory Failure

The Acute Physiology and Chronic Health Evaluation II (APACHE II) is the most widely used scoring systems in intensive care units in China and abroad. The APACHE II score is closely associated with disease severity and can predict mortality in patients. A number of studies have shown that the scores in patients with respiratory failure due to pulmonary TB are between 16.8 and 22.8 and this APACHE II score indicates a mortality rate of 20–50 % (Knaus et al. 1985). But the actual mortality was 59–69 %, which indicates the APACHE II scoring system may not be so accurate for patients with pulmonary TB and a prognosis for respiratory failure (Zahar et al. 2001; Silva et al. 2010; Lee et al. 2003; Erbes et al. 2006; Ryu et al. 2007).

16.3 TBICU Requirements

The settings of TBICUs vary among geographic regions and hospital sizes. The following basics are required: a dedicated, separate space with a reasonable layout; sufficiently experienced and specially trained healthcare workers; a comprehensive monitoring technology support system; and air purification devices (Cai 2006).

Most patients in the TBICU have respiratory failure as result of pulmonary TB. TBICUs should pay particular attention to the air handling systems. Negative pressure laminar flow systems should be established in ICUs in first-class hospitals (WHO 1999). The double door entrance to the TBICU should include an airlock and should be designed to restrict access to authorized personnel only. The inner doors of the air-lock chamber should remain locked until the outer doors of the chamber are closed. Air filtration or disinfection equipment is required in the air-lock chamber. The directional flow of air in the TBICU should be controlled by positive pressure and the incoming air should pass through a laminar flow device. The air handling system should be able to maintain the air at appropriate temperature and humidity, with a reasonable distribution of pressure and airflow throughout the interior (WHO 1999). In order to ensure a low level of pathogenic microorganisms within the unit, the total air volume should be replaced 10–15 times per hour, dust particles should be kept below 100,000 parts/m^3, the temperature should be between 22 and 24 °C, and the relative humidity should be maintained between 55 and 75 %. The unit should be disinfected by ozone or UV (>10 uW/m^3, 1–2 h) every 24 h. There should be at least 15–20 m^2 of floor space for every sick bed and there should be at least 1.5–3 m between beds to decrease the chance of cross-infection (Cai 2006). An intensive care unit setup for a single individual would require approximately 20–30 m^2 (Cai 2006), and can be used for isolating and treating drug-resistant TB patients. The exhale end of the respirator requires filtration. Closed suction tubes and a closed suction system should be used. Patient mouth, nose, and respiratory tract secretions must be strictly controlled and sterilized before disposal to prevent releasing TB into the environment. All materials contaminated by respiratory tract secretions must be sterilized.

TBICU staff, including doctors, nurses, care workers, and cleaners, must be trained in TB infection control measures. The changing of clothes and shoes and the wearing of N95 masks and hats before entering the TBICU must be strictly enforced. A hand washing system which requires hand washing before and after checking each patient, before technical procedures, after handling waste, and when entering or leaving the intensive care unit must be instituted.

16.4 Monitoring of Critical TB

16.4.1 Routine Clinical Monitoring

16.4.1.1 Symptoms

Coughing and Expectoration

The character of coughing and expectoration should be observed, including the time occurred, tone, intensity of coughing, expectoration volume, and expectoration character. An increase of expectoration volume indicates severe infection. A sudden decrease in amount of expectoration may be related to inadequate airway

humidification. Yellow purulent expectoration is suggestive of bacterial infection. Foul-smelling expectoration indicates anaerobic infections. Pink foamy expectoration may be pulmonary edema (Cai 2006). The amount and color and impurities of hemoptysis should also be observed.

Dyspnea

The respiratory rate should be observed, including breath depth and rhythm and whether there is orthopnea or use of accessory muscles of inspiration.

Chest Pain

The location and character of chest pain should be observed. Pneumothorax, acute pleurisy, and pulmonary embolism often result in severe pain in the affected side. The pain of angina and myocardial infarction or esophagus, mediastinal disorders always located in the precordium or breastbone.

16.4.1.2 Physical Signs

In order to adjust treatment as needed, the physical signs of critical TB patients should be monitored in TBICU, including continuous monitoring of vital signs and transcutaneous pulse oxygen saturation. Timely physical examinations of organ systems should also be performed.

Body temperature should be closely monitored. Choose the temperature measuring method/device according to the patient's disease condition: underarm thermometer, oral or rectal thermometer, nasopharyngeal temperature probe, continuous measurement of skin temperature, etc. A rise in body temperature will increase oxygen consumption and carbon dioxide production and can damage the central nervous system to delirium and coma. A drop in temperature can result in circulatory disturbance, hypoxia, or even ventricular fibrillation.

Breath should be monitored for the depth of breathing exercise, respiratory rate, rhythm, symmetry, and whether spontaneous breathing and mechanical ventilation are coordinated.

Pulse rate should be monitored along with pulse rhythm, tension, strength/weakness, and whether waveforms are symmetric.

Blood pressure can be monitored by noninvasive or invasive means (see Sect. 16.4.6). Arterial blood pressure and cardiac output have a direct relationship with total peripheral resistance. These factors reflect the heart afterload, myocardial oxygen consumption, and perfusion pressure. They are useful indicators to determine the circulation, but not the only indicators.

Transcutaneous pulse oxygen saturation (SpO_2) is monitored with a percutaneous pulse oximeter placed at the end of the finger, earlobe, etc. Infrared light sensors measure oxygenation levels of hemoglobin, which continuously and instantaneously

monitor blood oxygen saturation (SpO_2) which has a high correlation (normal greater than 95 %) with the patient's actual arterial oxygen saturation (SaO_2). The main factors affecting the percutaneous SpO_2 measurement are peripheral perfusion status and the color and/or thickness of keratinized layer of skin where the pulse oximeter is placed (Cai 2006).

Skin and mucous membranes should be observed for temperature, elasticity, and presence of any edema or hemorrhage. Note skin color with or without jaundice.

Observe patient's head and neck; pay attention to the eyes and note whether there is jaundiced sclera or edema of the conjunctiva. Observe jugular vein filling, tracheal position, neck lymph nodes, and thyroid.

Heart rate and rhythm should be noted along with whether heart sounds are strong or weak, whether there is heart murmur or other abnormal heart sounds, and the size of any cardiac dullness.

Lungs: note thorax morphology, respiratory rate, rhythm, and breathing movement symmetry. On percussion, note areas of drumlike sound or dullness or percussion drum so. On auscultation, note the nature, location, and phase of rales or pleural friction rub.

Abdomen: watch for abdominal distention, mass, ascites, tenderness, and/or rebound tenderness, and change in bowel sounds. Note liver and spleen size.

16.4.1.3 Fluid Intake and Output

Urine is an important indicator of heart and kidney function. Record daily intake and output fluid volume to monitor fluid balance. Decreased urine output (positive balance) should be considered a sign of inadequate intake, shock, renal insufficiency, or urinary retention (Cai 2006). Electrolyte balance should be maintained if urine output increases.

16.4.2 Nutritional Status Monitoring

In patients with critical TB, correct evaluation of nutritional status and the implementation of sound nutritional support is an important prerequisite. Methods include patient inquiry (perform a detailed investigation of the patient's daily diet, lifestyle, and economic conditions), observation (note the presence or absence of weight loss, muscle weakness, reduced body fat, dehydration or edema, and whether hair is sparse and/or lacks luster), and physiological measurements. There are many physiological indicators of nutritional status. Each has its limitations; combine a number of indicators to better evaluate the nutritional status of the patient.

Body mass index (BMI) is calculated by dividing the patient weight (kg) by height squared (m^2). A normal male BMI is 20–25, and less than 20 may be underweight. A normal female BMI is 19–24 and less than 19 may be underweight (Zhang and Gao 2006; Jiang 2008).

Triceps skinfold thickness (TSF) reflects the storage of body fat. To measure, keep patient's left upper arm down and relaxed. Find the midpoint of the triceps between the top of the shoulder (acromion) and the elbow (olecranon). Pinch the skin with the left thumb and index finger to make a vertical skinfold 1 cm from the measurement point and measure with calipers. Normal adult measurements are 12.5 mm for males and 16.5 mm for females. Measured values of 80–90 % of normal indicates mild malnutrition; 60–80 % indicates moderate malnutrition; below 60 % indicates severe malnutrition (Zhang and Gao 2006; Jiang 2008).

Mid Upper Arm Circumference (MUAC) includes upper arm muscles and any subcutaneous fat, and reflects nutritional status. Keep left upper arm hanging down and relaxed. At the midpoint between the acromion and the olecranon, measure the girth of the arm with a soft tape (Zhang and Gao 2006; Jiang 2008).

Arm muscle circumference (AMC) reflects the somatic protein status. AMC is calculated from the MUAC and TSF measurements above (in centimeters) as follows:

$$\mathrm{AMC} = \mathrm{MUAC} - \left(3.14 * \mathrm{TSF}\right)$$

Normal AMC is 25.3 cm for males and 23.2 cm for females. A measurement equivalent to 80–90 % of normal indicates mild malnutrition, 60–80 % indicates moderate malnutrition, and less than 60 % indicates severe malnutrition. AMC closely relates to serum albumin levels. If the patient's serum protein is less than 28 g/L, AMC is also decreased in about 87 % of patients (Zhang and Gao 2006; Jiang 2008).

Serum protein, transferrin, prealbumin, and other indicators may be useful as part of a comprehensive evaluation, but care should be taken in interpretation, as these are variable indicators of stress, infection, and hypoxia effects.

Creatinine Height Index (CHI) is calculated by dividing the 24-h urine creatinine excretion (mg) by patient height (cm). In the case of constant protein intake, a result of less than 6.0 indicates that there is a protein deficiency (Zhang and Gao 2006; Jiang 2008).

The Absolute Lymphocyte Count normal value is 1.5×10^9 cells/L. A count of less than 1.2×10^9 cells/L may indicate malnutrition or immune dysfunction (Zhang and Gao 2006; Jiang 2008).

16.4.3 Brain Function Monitoring

General brain function monitoring includes checking consciousness, language ability and mental status, pupil size and light reflex, and limb activity and muscle tone. Use the Glasgow Coma Score (GCS) for assessment in adult patients. A GCS of less than or equal to 8 is indicative of severely damaged brain function (see Table 16.1).

Intracranial pressure (ICP) is the pressure of the cranial cavity and thus cerebrospinal fluid and brain tissue. Normal (lateral position) ICP is 5–15 mmHg in adults, 3.5–7.5 mmHg in children. Increased ICP (more than 15 mmHg) is common in severe tuberculous meningitis. Currently, ICP is measured invasively. A hole is

Table 16.1 Glasgow coma score (GCS) (Teasdale and Jennett 1974)

Points	Motor response	Language response	Eye response
6	Moves as requested		
5	Purposeful movements toward pain	Oriented	
4	Withdrawal from pain	Confused	Active eyes
3	Flexion in response to pain	Random or inappropriate words	Eyes open in response to speech
2	Hyperextension in response to pain	Incomprehensible sounds	Eyes open in response to pain
1	No motor response	No verbal response	Cannot open eyes

Interpretation of GCS total to evaluate brain injury: minor at 13 or more, moderate at 9–12, severe if less than 9

drilled into the skull and a catheter with a pressure sensor is placed in the ventricle or in the subdural, epidural, or subarachnoid space. ICP measured by intraventricular catheter is currently considered the most accurate and reliable and allows direct discharge of cerebrospinal fluid to reduce ICP. ICP monitoring may leave the patient vulnerable to intracranial infections. Great care should be taken during prep and catheter insertion to minimize infection, and catheter time should generally be limited to less than 72 h (Liu and Yan 2009).

Electroencephalography (EEG) uses scalp electrodes to monitor brain activity. Though not required, EEG can be used to monitor critical TB symptoms of the central nervous system, including coma. Increased intracranial pressure shows mainly on the EEG as abnormalities of diffuse slow activity in the context of simultaneous attacks on both sides with high volatility of θ or δ rhythm. EEG manifestations of pulmonary encephalopathy are characterized by diffuse abnormalities, mainly α irregular, slow, diffuse δ or θ wave to the forehead. A resting EEG with no electrical activity is one of the diagnostic criteria of brain death (Liu and Yan 2009).

16.4.4 Monitoring of Respiratory Function

Basic monitoring of respiratory function includes checking vital signs, respiratory rate, respiratory motion, breath sounds, and peripheral circulation and other limbs.

16.4.4.1 Lung Capacity Monitoring

Static lung capacity and tidal volume should be monitored to detect changes. Common indicators include inspiratory reserve volume (IRV), expiratory reserve volume (ERV), functional residual capacity (FRC), vital capacity (VC), total lung capacity (TLC), and the residual volume/total lung capacity ratio (Cai 2006).

16.4.4.2 Lung Function Monitoring

The determination of pulmonary ventilation can be more meaningful than lung volume measurements because it can reflect dynamic changes in pulmonary ventilation. Common monitoring indicators include minute ventilation (V_E), maximal voluntary ventilation (MVV), forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), etc.

The dead space volume/tidal volume ratio (V_D/V_T) reflects alveolar ventilation. Normal values range from 20 to 40 %. The ratio can be calculated using the Bohr equation

$$\frac{V_D}{V_T} = \frac{\left(PaCO_2 - P_ECO_2\right)}{PaCO_2}$$

where P_ECO_2 is the partial pressure of expired CO_2 (Zhang and Gao 2006).

16.4.4.3 Pulmonary Ventilation Function Monitoring

Measures of pulmonary ventilation include the ventilation/perfusion (V/Q) ratio, alveolar-arterial oxygen gradient ($A\text{-}aO_2$) which may show hypoxia, Oxygen delivery (DO_2) which shows oxygen delivered over time, and the oxygenation index. The ratio PaO_2/FiO_2 is one of the main monitoring indicators of pulmonary ventilation; the calculation is simple, and the normal range 430–560 mmHg. Combined with medical history and other indicators, $PaO_2/FiO_2 < 300$ mmHg suggests acute lung injury (ALI) and $PaO_2/FiO_2 < 200$ mmHg is a sign of acute respiratory distress syndrome (ARDS) (Cai 2006; Zhang and Gao 2006; Yu 2008).

16.4.4.4 Respiratory Muscle Function Test

Maximum inspiratory pressure (MIP) reflects the overall strength of inspiratory muscles. Maximum expiratory pressure (MEP) reflects the expiratory muscle strength and overall ability to cough and expectorate. Maximum transdiaphragmatic pressure (Pdimax) evaluates diaphragm function (Zhang and Gao 2006; Yu 2008).

16.4.4.5 Blood Gas Monitoring

Noninvasive monitoring of pulse oxygen saturation (SPO_2) is important. Normal SPO_2 is 95–100 % while breathing normal air, and has good correlation with SaO_2 ($\gamma = 0.9$). Simple, noninvasive, continuous display of arterial oxygen saturation and pulse waveform monitoring is extremely important in critically ill patients (Cai 2006).

End-tidal carbon dioxide partial pressure (PetCO2) has a good correlation with $PaCO_2$ and can be measured by an artificial airway gas sampling device which continuously monitors exhaled CO_2. Normal $PetCO_2$ is 35–40 mmHg. This data can be affected by the CO_2 volume produced by the tissue, pulmonary blood flow (cardiac output), alveolar ventilation, and other factors. It may indirectly reflect changes in these indicators (Cai 2006).

16.4.5 Ventilator Monitoring

Respiratory failure is a serious complication of TB. Ventilator technology and mechanical lung ventilation has become an important therapeutic treatment for respiratory failure. Ventilator monitoring is very complex and important; any changes of parameter could not only infect the pulmonary ventilation function, but also influence hemodynamics and organ function.

16.4.5.1 Artificial Airway Monitoring

Endotracheal intubation should be checked for proper depth and stability, and balloon pressure should be monitored. Maximum balloon pressure is maintained at 20–25 mmHg. Too high a pressure can lead to tracheal mucosal ischemia or necrosis; too low a pressure can lead to leakage and aspiration of oropharyngeal secretions (Yu 2008).

16.4.5.2 Ventilation Monitoring

Include tidal volume and minute ventilation. Tidal volume is usually set to 5–12 mL/kg; adult minute ventilation can be set to 6–10 L/min. The ventilator, which has the function of monitoring exhaled carbon dioxide, can monitor the amount of dead space/tidal ratio (V_D/V_T) as discussed in Sect. 16.4.4.2.

16.4.5.3 Monitoring of Respiratory Mechanics

Peak inspiratory pressure (PIP) is the maximum pressure in the respiratory cycle of mechanical ventilation. Mechanical ventilation with a high PIP is related to barotrauma; PIP should generally be limited to below 40 cmH_2O (Zhang and Gao 2006; Yu 2008).

Plateau pressure (Pplateau), also called end-inspiratory pressure, depends on the factors of tidal volume and respiratory system compliance. If tidal volume is stable, the worse the respiratory system compliance, the higher the plateau pressure. Set some pause time on the ventilator to display the end-inspiratory plateau pressure, to reflect the respiratory system compliance indicators.

End-expiratory pressure (EEP) is the sum of setting positive end-expiratory pressure (PEEP) and endogenous PEEP ($PEEP_i$). If the patient's end-expiratory airway pressure cannot return to zero or the setting PEEP level, the excess pressure from the lungs' failure to empty is called the endogenous PEEP value. $PEEP_i$ is caused by increased airway resistance due to trapped gasses or too short an expiratory time which is then inadequate to complete breath-related activity and is not conducive to patient ventilation.

Airway resistance pressure (Praw) is the resistance to airflow in the patient's respiratory tract that must be overcome by mechanical positive pressure ventilation. P_{raw} and plateau pressure combined constitute peak inspiratory pressure. Increased P_{raw} may be a sign of retention of airway secretions.

Airway resistance (Raw) equals P_{raw} divided by the flow rate. Normal airway resistance is in the range of 0.6–2.4 $cmH_2O/(L\ S)$. The airway resistance of an endotracheal intubation patient is up to 6 $cmH_2O/(L\ S)$; the airway resistance of a bronchial asthma patient is up to 3–18 $cmH_2O/(L\ S)$ (Zhang and Gao 2006; Yu 2008).

Compliance refers to the changes in capacity produced by pressure changes and reflects the elasticity of the lungs. Compliance can be static or dynamic according to different methods of detection.

Static compliance (C_{st}) or respiratory system compliance (C_{rs}), including lung and thoracic compliance, is measured when there is no airflow (during inspiratory pause).

$$C_{st} = \frac{V_T}{\left(P_{plateau} - \text{PEEP}\right)}$$

Dynamic compliance (C_{dyn}) is measured when there is airflow and includes lung compliance and airway resistance factors.

$$C_{dyn} = \frac{V_T}{\left(\text{PIP} - \text{PEEP}\right)}$$

16.4.5.4 Mechanical Ventilation Waveform Monitoring

Waveform displays allow real-time observation of respiratory mechanics. This gives the medical staff a better understanding of patient pathophysiology characteristics. Ventilation settings can be reasonably adjusted in order to achieve better therapeutic effect. Mechanical ventilation waveform displays include the pressure–time curve, volume–time curve, flow rate–time curve, the pressure–volume loop, and flow rate–volume loop.

The pressure–time curve reflects airway pressure changes over time period in real time. This curve reflects PIP, $P_{plateau}$, P_{raw}, and PEEP changes (Yu 2008; see Fig. 16.1).

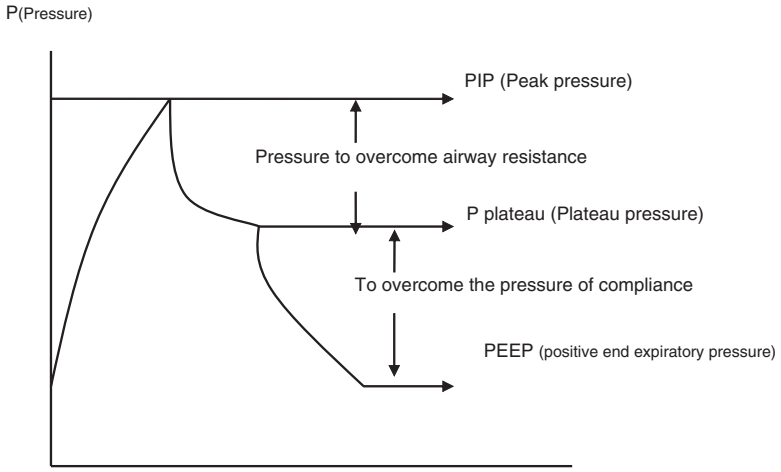

Fig. 16.1 Relationship of pressure–time curves and airway resistance and compliance

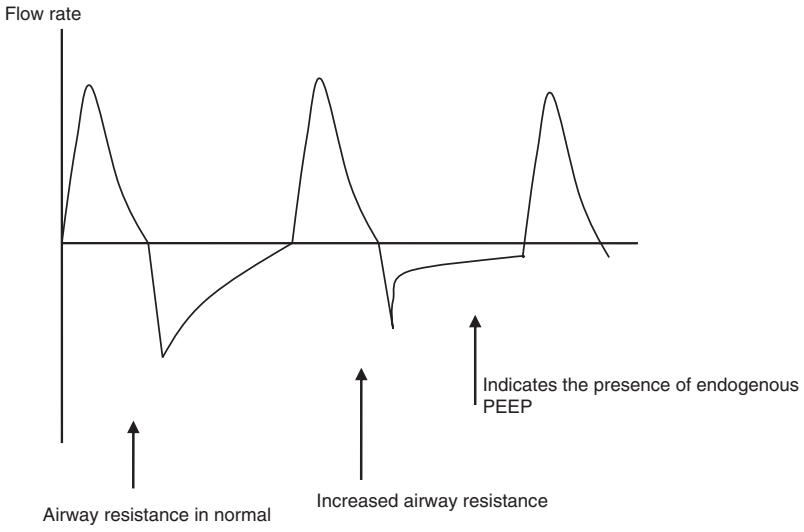

Fig. 16.2 Airway resistance effects on the flow rate–time curve

The volume–time curve reflects the tidal volume changes in the ventilation cycle.

The flow rate–time curve reflects the flow rate of the inspiratory phase and expiratory phase in the ventilation cycle. When patients present with obstructive ventilatory dysfunction, peak expiratory flow rate decreases and the flow rate quickly slows down. The curve shows a shaped bend and extension of the expiration time. The end-expiratory flow rate cannot be reduced to 0, and the tips at the end of exhalation indicate the presence of $PEEP_i$ (Yu 2008). See Fig. 16.2.

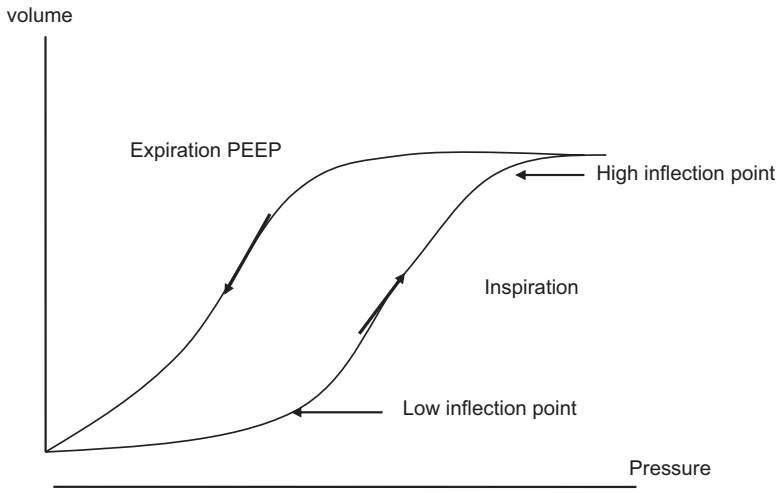

Fig. 16.3 Pressure–volume loop of ARDS patients, low and high inflection point

The pressure–volume loop is formed by the changes of inspiratory phase and expiratory phase in the breathing cycle. Real-time monitoring of the volume related to the mechanical ventilation pressure changes reflects lung compliance. The low inflection point indicates when opening pressure is reached and the alveoli begin to expand. This inflection point is used to select the best PEEP, which is generally more than 2 cmH_2O. The high inflection point reflects the degree of chest flexibility at maximum expansion. High pressure of mechanical ventilation should be lower than the high pressure inflection point in order to avoid barotrauma and circulatory function suppression (Yu 2008; see Fig. 16.3).

The flow rate–volume loop tracks airflow rate and volume changes in a respiratory cycle. This loop reflects the set flow rate type (constant, decreasing type, etc.) in inspiratory phase, and can indicate a probable increased airway resistance in the expiratory phase, gas trapping, or pipeline leak. See Fig. 16.4 (Yu 2008).

16.4.6 Hemodynamic Monitoring

16.4.6.1 Arterial Blood Pressure (ABP) Monitoring

In cases of severe hypotension, invasive blood pressure monitoring is more accurate than noninvasive blood pressure monitoring. It is usually performed via arterial puncture of the radial artery or the dorsal artery in the foot. Some of the indications are severe shock, hypotension, individuals taking vasoactive drugs, and individuals needing frequent arterial blood gas examination. Some common complications of invasive blood pressure monitoring are infection, embolisms, hemorrhaging, and aneurysms.

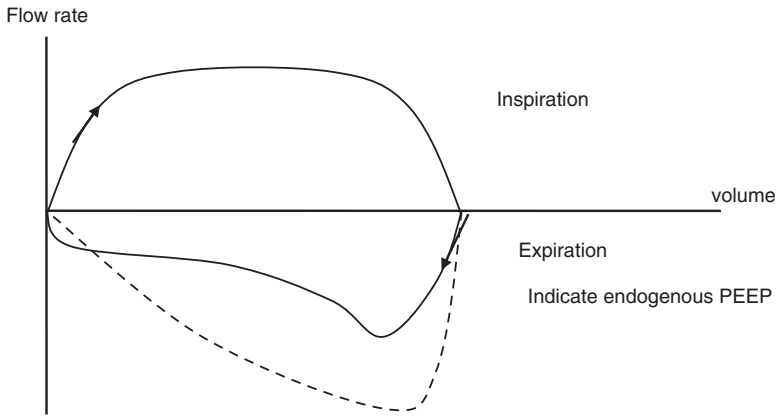

Fig. 16.4 Flow rate–volume loop of increased airway resistance. *Dotted line* is the normal expiratory tracing

16.4.6.2 Central Venous Pressure Monitoring

Central venous pressure (CVP) is the pressure in the chest section when the blood flows through the right atrium and the inferior vena cava. This measurement mainly reflects the right ventricular preload. Normal CVP is 4–12 mmHg. CVP is a function of blood volume, level of cardiac function, venous tone, intrathoracic pressure, venous return flow, and pulmonary vascular resistance, among other factors. Causes and treatment of abnormal central venous pressure are shown in Table 16.2. CVP is an indirect indicator of cardiac function. Therefore, continuous observation of dynamic changes is more meaningful than a single absolute value.

16.4.6.3 Pulmonary Artery Pressure and Pulmonary Capillary Wedge Pressure Monitoring

Insert a floating catheter (Swan-Ganz catheter) through the superior vena cava or inferior vena cava, then through the right atrium and right ventricle and into the pulmonary arteries. This allows measurement of the right atrial pressure (RAP), right ventricular pressure (RVP), pulmonary artery systolic pressure (RADP), mean pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP). When the left ventricle and mitral valve function is normal, pulmonary capillary wedge pressure is only 1–2 mmHg higher than left atrial pressure, so pulmonary capillary wedge pressure can be used to estimate the state of pulmonary circulation and left ventricular function. It is also a useful and reliable indicator of left ventricular preload. In pulmonary arteries the normal systolic pressure is 15–30 mmHg, the diastolic pressure is 6–12 mmHg, the mean pressure is 9–17 mmHg, and the PCWP is 6–12 mmHg. A PCWP < 6 mmHg can indicate a serious shortage of vessel capacity; a PCWP of 12–15 mmHg indicates a normal vessel capacity or an insufficient

Table 16.2 Causes and treatment of central venous pressure changes (Liu and Yan 2009)

CVP	Arterial pressure	Cause	Treatment
Low	Low	Hypovolemia	Add blood volume
Low	Normal	Good heart function, low blood volume	Appropriate to add blood volume
High	Low	Poor cardiac function, reduced cardiac output	Administer cardiac stimulant, oxygen, diuretics, and/or vasodilator. Correct acidosis. Carefully control fluid intake
High	Normal	Excessive contraction of vascular capacity, pulmonary vascular resistance increased	Control fluid intake, increase vascular and pulmonary capacity with a vasodilator
Normal	Low	Reduced cardiac ejection function, excessive contraction of capacity vessels	Perform cardiac infusion test. In cases of hypovolemia, infuse fluid

vessel capacity with left ventricular dysfunction; a PCWP > 15 mmHg indicates too much vessel capacity or left ventricular dysfunction with an associated risk of pulmonary edema (Yu 2008; Liu and Yan 2009).

16.4.6.4 Cardiac Output (CO) Monitoring

Cardiac output is defined as the total volume of blood pumped by one ventricle per minute (normal left and right ventricular output is basically the same). CO is an important indicator of cardiac function. A Swan-Ganz catheter can be used with the thermal dilution method to measure cardiac output. This is done by injecting cold saline solution into the right atrium and measuring the blood temperature change as it passes the catheter tip in the pulmonary artery. One can then calculate the right ventricular output. There are four factors that affect cardiac output: myocardial contractility, cardiac preload, cardiac after load, and heart rate. Normal CO is 4–8 L/min and is expressed as

$$CO = SV * HR$$

where SV is ventricular stroke volume and HR is heart rate. Other hemodynamic parameters can be derived from CO.

Cardiac index (CI) more accurately reflects heart function by factoring in the effect of body size (represented by body surface area, BSA) when estimating cardiac output.

$$CI = \frac{CO}{BSA}$$

The reference value for CI in a healthy population is 2.5–4 L/(min m^2). A cardiac index of <2.5 L/(min m^2) indicates heart failure, and if the CI falls below 1.8 L/(min m^2) the patient may be in cardiogenic shock.

Stroke volume (SV) and stroke index (SI) reference values in a healthy population are 60–130 mL and 35–55 mL/m^2, respectively.

Pulmonary vascular resistance (PVR) must be overcome for blood to flow through the circulatory system. A normal PVR is 10~25 (kPa s)/L. Elevated PVR is associated with pulmonary vascular disease, lung disease with pulmonary hypertension and hypoxemia. Dynamic monitoring of PVR is beneficial to understanding disease progression. *Pulmonary vascular resistance index (PVRI)* is indexed to body mass. A normal PVRI is 22.5–31.4 (kPa S)/(L m^2) (Liu and Yan 2009).

Systemic vascular resistance (SVR) is used in the diagnosis of vascular disease. The reference value for SVR is 90–150 (kPa s)/L. The reference value for *systemic vascular resistance index (SVRI)*, which is the SVR over body surface area, is 195–240 (kPa S)/(L m^2) (Liu and Yan 2009).

16.4.6.5 Pulse Indicator Continuous Cardiac Output (PiCCO) Monitoring

PiCCO is a simple technology that uses hyperactivity dilution and pulse wave contour analysis to continuously and accurately monitor cardiac output (see a list of parameters in Table 16.3). This technology, which was developed more than 10 years ago, is widely used in critically ill patients requiring hemodynamic monitoring. Because PiCCO does not require the use of a pulmonary artery catheter, the cost and risk to patients are reduced. Instead, PiCCO uses a central venous catheter and a femoral artery catheter to monitor cardiac output in both adults and children. PiCCO can be used in patients requiring cardiovascular and circulatory volume status monitoring such as after transplant surgery and in cases of shock, cardiac dysfunction, sepsis, and/or acute respiratory distress syndrome (ARDS). Single measurement methods for estimating cardiac output have given way to stroke-based continuous cardiac output monitoring methods such as PiCCO (Fig. 16.5). For normal ranges for main PiCCO parameters, see Table 16.4.

PiCCO is contraindicated in patients with complications such as hemorrhagic disease, aortic aneurysm, arteritis, arterial stenosis, limb embolism, lung resection, pulmonary embolism, cardiopulmonary bypass, unstable body temperature or blood pressure, severe arrhythmia, severe pneumothorax, heart and lung compression disorders, heart cavity cancer and/or a heart shunt.

Due to PiCCO's quick response time and convenience, it is possible to make timely comparisons and judgments from multiple hemodynamic data. Intrathoracic blood volume (ITBV) gives a better estimate of heart preload than the right ventricular end-diastolic pressure (RVEDP) and CVP and shows better accuracy. If catecholamines, mechanical ventilation, or other parameters are changed, the intrathoracic blood volume index (ITBVI) can reflect changes in preload. Extravascular lung water (EVLW) is a measure of pulmonary interstitial fluid volume, and is a more accurate indicator in the diagnosis and treatment of pulmonary edema than PCWP.

Table 16.3 Main parameters of PiCCO (Yu 2008; Liu and Yan 2009)

Thermodilution parameters (single measurement)	Parameters of pulse contour (continuous measurements)
Cardiac output (CO)	Pulse continuous cardiac output (PCCO)
Global end-diastolic volume (GEDV)	Stroke volume (SV)
Intrathoracic blood volume (ITBV)	Heart rate (HR)
Extravascular lung water (EVLW)	Stroke volume variation (SVV)
Pulmonary vascular permeability index (PVPI)	Arterial pressure (AP)
Cardiac index (CFI)	Systemic vascular resistance (SVR)
Global ejection fraction (GEF)	Maximum slope of arterial pressure (dPmx)

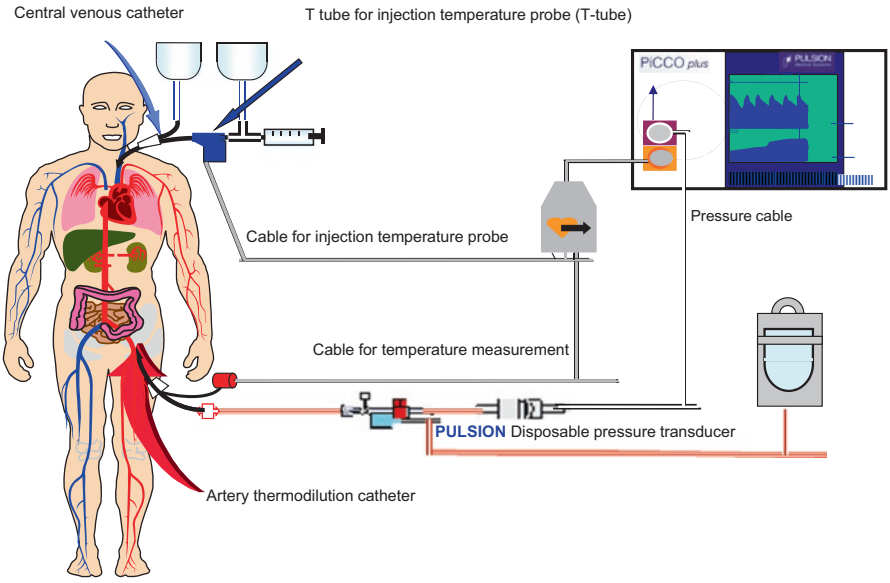

Fig. 16.5 PiCCO tubing connection diagram (Yu 2008)

Table 16.4 Normal values of PiCCO parameters (Yu 2008; Liu and Yan 2009)

Parameters	Normal range	Unit
Cardiac index (CI)	3.0–5.0	L/min/m^2
Stroke volume index (SVI)	40–60	mL/m^2
Global end-diastolic volume index (GEDI)	680–800	mL/m^2 mL/m^2
Thoracic blood volume index (ITBI)	850–1000	mL/kg
Extravascular lung water index (ELWI)	3.0–7.0	mL/kg
Pulmonary permeability index (PVPI)	1.0–3.0	
Stroke volume variation (SVV)	≤10	%
Global ejection fraction (GEF)	25–35	%
Cardiac function index (CFI)	4.5–6.5	1 min^{-1}
Mean arterial pressure (MAP)	70–90	mmHg
Systemic vascular resistance index (SVRI)	1700–2400	(kPa S)/(L m^2)

16.4.7 Gastrointestinal Mucosal pH (pHi) Monitoring

Given the importance of the gastrointestinal mucosal barrier and its vulnerability due to the effects of ischemia and hypoxia, steps should be taken to protect the gastrointestinal mucosa of critical TB patients. Because ischemia and hypoxia can lead to local tissue lactic acid accumulation and acidosis, the measurement of acidity in the gastrointestinal mucosa may be an alternative indicator of tissue perfusion and oxygen metabolism. The pHi is assessed by gastric tonometry, which measures the gastric partial pressure of carbon dioxide in the stomach, and then converts it to pHi. A normal pHi ranges from 7.35 to 7.45. The risk of MODS and mortality significantly increases when the pHi < 7.32 (Liu and Yan 2009).

16.4.8 Chest X-ray Monitoring

Chest X-ray monitoring is used to monitor the progress of lung disease, the placement of artificial airways, the positioning of central venous catheters, and as a reference value to determine removal from the ventilator.

16.4.9 Liver and Kidney Function Monitoring

Severe chronic consumption, infection, shock, and anti-TB drug treatment can have significant impacts on renal and hepatic function in critical TB patients, so close monitoring is critical.

16.4.9.1 Monitoring of Renal Function

The simplest method to evaluate renal function and the dilution and concentration function of renal tubules is by measuring the specific gravity of the urine.

Glomerular filtration rate assessment includes monitoring values for endogenous creatinine clearance (CCR), creatinine (Cr), and blood urea nitrogen (BUN). However, serum β2-microglobulin (β2-M) levels give a better estimate of the glomerular filtration rate. The glomerular filtration rate and β2-M are negatively correlated; when the glomerular filtration rate decreases, β2-M begins to rise earlier and more significantly than the serum creatinine concentration (Cai 2006; Yu 2008).

16.4.9.2 Monitoring of Hepatic Function

Protein metabolism is one of the liver's major functions. The liver produces albumins, glycoproteins, lipoproteins, and a variety of transporter proteins. When mononuclear cells in the liver are stimulated, γ-globulin is overproduced. This condition

can progress to autoimmune hepatitis, which can lead to hyperthyroidism and other endocrine system dysfunction. Therefore, it is important to monitor levels of serum albumin, immune globulin, and lipoprotein. Most critical TB patients have severe hypoproteinemia.

Glucose metabolism plays an important role in maintaining stable blood sugar levels. Abnormal blood sugar levels can be indicative of dysfunctional glucose metabolism caused by substantial liver damage.

Lipid monitoring is another way to track hepatic function. The liver synthesizes endogenous cholesterol, fatty acids, triglycerides, and other lipids. It also clears exogenous lipids and adipose tissue fatty acid, and decomposes free fatty acid. The liver also synthesizes high-density lipoprotein (HDL), very low density lipoprotein (VLDL), and lecithin—cholesterol acyl transfer enzymes (LCAT).

Bilirubin metabolism is another indicator of liver function and can be monitored by checking serum total bilirubin, 1 min bilirubin test, urine bilirubin, urobilinogen, etc.

Serum enzymes that can also be indicators of liver function include alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), γ-glutamyl transferase (GGT) and its isoenzymes, and cholinesterase.

16.4.10 Coagulation Monitoring

Ninety percent of critical TB patients exhibit the formation of microvascular thrombosis due to endothelial cell dysfunction, insufficient endogenous anticoagulant and thrombosis formation materials, changes in platelet quality and quantity, suppressed bone marrow function, leukocyte adhesion, decreased red blood cell deformability in individuals prone to disseminated intravascular coagulation (DIC), small artery thrombosis associated with ischemia and hypoxia, or hyperfibrinolysis caused extensive bleeding in late stage so that tissue perfusion is in serious deficiency. This accelerates organ dysfunction (Cai 2006; Yu 2008).

It is important to monitor bleeding and clotting time, prothrombin time (PT), and activated partial thromboplastin time (APTT). In patients prone to DIC, it is necessary to perform the 3P test, and to monitor quantitative plasma fibrinogen, fibrin degradation products (FDP), and, when necessary, the patient's clotting factor levels.

16.4.11 Arterial Blood Gas and pH Monitoring

Arterial blood gas analysis and monitoring includes assessment of the patient's oxygenation, gas exchange, and acid–base status. It is performed by collecting arterial blood from the radial artery, dorsal artery, or the femoral artery via direct puncture or through an arterial catheter. The blood analysis data is combined with patient history and clinical examination results.

16.5 Treatment of Critical TB

16.5.1 Anti-TB Treatment

Many studies indicate that delayed treatment of TB patients with active TB reduces the survival rate (Pablos-Méndez et al. 1996; Rao et al. 1998; Sacks and Pendle 1998). For patients with critical TB, delayed anti-TB treatment is also independently associated with factors increasing hospital mortality (Zahar et al. 2001; Ryu et al. 2007). Therefore, patients with critical TB should be started on effective anti-TB treatment as soon as possible if organ function allows. Because of the stress put on the major organs of patients with critical TB, the incidence of MODS can reach 19–80 % (Zahar et al. 2001; Lee et al. 2003; Erbes et al. 2006; Ryu et al. 2007; Chen and Zhu 2010; Silva et al. 2010). Therefore, an anti-TB treatment regimen should be based on the extent of TB disease and the state of liver and kidney function. Likewise, it is important to frequently monitor liver and kidney function during treatment.

Newly diagnosed individuals (and some patients receiving re-treatment) with mild hepatic dysfunction may choose a treatment protocol which includes one drug with potential liver toxicity. For instance, rifampicin can be substituted with rifapentine in the following regimens: isoniazid, rifapentine, ethambutol, and ofloxacin; or rifapentine, ethambutol, and ofloxacin solution. Alternatively, based on the type of TB, one can select multiple drugs with liver toxicity but at the same time administer liver protecting treatment. If there are a number of abnormalities in liver function during treatment, especially levels of transaminase 2 × the upper normal limit, alkaline phosphatase 1.5 × normal, and an increase in bilirubin, TB treatment should be withdrawn immediately and steps taken to protect the liver (American Thoracic Society 2003; Ma and Zhu 2006).

For patients with renal dysfunction, the therapeutic course of treatment should be consistent with initial and recurrent TB. However, this requires careful design of a drug treatment program with the inclusion of toxic and nontoxic drugs and constant adjustment of drug dosages to maintain renal function. Rifampicin and isoniazid are metabolized by the liver so do not require dose adjustments. Although pyrazinamide is metabolized by the liver, its metabolites (pyrazine acid and 5-hydroxy-pyrazine acid) accumulate in patients with renal insufficiency, so kidney function must be monitored closely. Ethambutol, streptomycin, kanamycin, amikacin, and capreomycin are mainly excreted by the kidneys, so their dosages must be adjusted based on renal function (American Thoracic Society 2003; Launay-Vacher et al. 2005). The pharmacokinetic characteristics of anti-TB drugs are concentration dependent, so dose adjustments are made primarily by extending the treatment interval (Launay-Vacher et al. 2005). The reduced dosages for patients with creatinine clearance of less than 30 mL/min and patients receiving hemodialysis treatment are similar. Details are shown in Table 16.5.

Almost 70 % of TB patients suffer severe hypoproteinemia (Silva et al. 2010), which may affect the absorption of anti-TB drugs and result in low plasma concentrations of rifampin and ethambutol in patients with severe TB. Factors such as liver

Table 16.5 Dosages of anti-TB drugs in adult patient with renal dysfunction and dialysis treatment (American Thoracic Society 2003)

Drug	Need to adjust the dosage?	Creatinine clearance values < 30 mL/min or dialysis treatment recommended dosage of drugs
Isoniazid	No	300 mg, 1 time/day or 900 mg/time, 3 times/week
Rifampicin	No	600 mg, 1 time/day or 600 mg/time, 3 times/week
Pyrazinamide	Yes	25–35 mg/kg/time, 3 times/week
Ethambutol	Yes	15–25 mg/kg/time, 3 times/week
Levofloxacin	Yes	750–1000 mg/time, 3 times/week
Cycloserine	Yes	250 mg, 1 time/day or 500 mg, 3 times/week
Ethionamide	No	250–500 mg, 1 time/day
Aminosalicylic	No	4 g, 2 times/day
Streptomycin	Yes	12–15 mg/kg, 2–3 times/week
Capreomycin	Yes	12–15 mg/kg, 2–3 times/week
Kanamycin	Yes	12–15 mg/kg, 2–3 times/week
Amikacin	Yes	12–15 mg/kg, 2–3 times/week

and kidney dysfunction and the metabolism of anti-TB drugs make it difficult to control the effective blood concentration and therapeutic effect of anti-TB drugs. Therefore, drug plasma concentration in patients with liver and kidney dysfunction should be monitored closely (Zahar et al. 2001; American Thoracic Society 2003).

16.5.2 Anti-infection Treatment

Nosocomial respiratory infections occurred in 20–69 % of patients with critical TB in hospital intensive care units (Zahar et al. 2001; Lee et al. 2003; Erbes et al. 2006; Ryu et al. 2007; Silva et al. 2010). In recent years, multidrug-resistant pathogens causing hospital-acquired pneumonia have also increased sharply, especially in intensive care units. The most common pathogens causing hospital-acquired pneumonia are aerobic, gram-negative bacteria, including *Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Acinetobacter* spp. Less common are gram-positive bacteria, such as *Staphylococcus aureus*, the majority of which are methicillin-resistant. Lower respiratory tract secretions must be collected for inspection before anti-infection treatment; however, treatment should not be delayed to collect samples in critically ill patients. In these cases, early broad-spectrum treatment should be based on trends of area pathogens with the goal of having the best anti-inflammatory effect. Once the culture results and clinical evaluation are clear, treatment should be promptly adjusted (American Thoracic Society and Infectious Disease Society of America 2005).

In addition to the use of antimicrobial drugs to control infection, attention should be paid to airway humidification, postural drainage of sputum, and the use of bronchial expectorants and diastolic drugs. Mechanical ventilation and intubation equipment should be replaced when wet, and suction should be used to ensure that

air bag pressure is greater than 20 cmH_2O and to prevent subglottic secretions from accumulating around the balloon into the lower airway. Also, patients should be kept in a semi-recumbent position to prevent aspiration of gastric reflux (American Thoracic Society and Infectious Disease Society of America 2005).

16.5.3 Mechanical Ventilation (MV) Treatment

Respiratory failure is a serious complication of TB, and the main reason for admittance into the ICU for the treatment of TB (Erbes et al. 2006; Silva et al. 2010). After years of development, ventilator technology and mechanical lung ventilation for the purpose of gas exchange has become an important therapeutic treatment for respiratory failure.

Mechanical ventilation can serve multiple purposes. It can correct respiratory acidosis by improving alveolar ventilation, $PaCO_2$, and pH. Usually the blood $PaCO_2$ and pH should be maintained at the level of remission. Mechanical ventilation can also be used to correct hypoxemia and alleviate tissue hypoxia by improving alveolar ventilation, increasing inspired oxygen concentrations, increasing lung volume, and reducing breathing power. The basic goal of mechanical ventilation is to improve oxygenation such that $PaO_2 > 60$ mmHg or $SaO_2 > 90$ %. Mechanical ventilation also reduces respiratory power and relieves respiratory muscle fatigue. In patients with respiratory failure due to TB, airway resistance is increased, pulmonary compliance is decreased, and endogenous end-expiratory pressure ($PEEP_i$) leads to a significant increase in respiratory work consumption. In addition, TB patients often have poor nutritional status, and patients with severe TB are prone to respiratory muscle fatigue. Mechanical ventilation can relieve respiratory muscle fatigue in these patients. Additionally, mechanical ventilation can help expectoration and control infection, allow the safe use of sedatives and muscle relaxants, and reduce intracranial pressure in patients with tuberculous meningitis by controlling hyperventilation (Yu 2008; Liu and Yan 2009).

Indications

- When conditions continue to deteriorate despite active treatment; symptoms of pulmonary encephalopathy appear; there is a disturbance of consciousness.
- There is a serious abnormity in breathing; a respiratory rate >35 or <6–8 breaths/min, respiratory rhythm abnormalities, spontaneous breathing becomes weak or disappears.
- Blood gas analysis shows severe ventilation and/or oxygenation disorder: after full oxygen therapy, $PaO_2 < 50$ mmHg and $PaCO_2 > 80$ mmHg and continuously increased, or arterial $pH \leq 7.20$ which indicates serious decompensated respiratory acidosis.

Contraindications for mechanical ventilation include previous occurrence of bullae, lung cysts, hemoptysis, acute myocardial infarction, or shock. Some believe that

treatment of active TB with invasive mechanical ventilation is contraindicative due to the risk of spreading TB by mechanical ventilation. However, there is no research to support the idea that positive pressure ventilation can lead to the spread of TB. Currently, there are no absolute contraindications for mechanical ventilation as long as the correct strategy is implemented and targeted to take appropriate measures.

16.5.3.1 Mechanical Ventilation Methods

Mechanical ventilation can be implemented invasively or noninvasively. Noninvasive positive pressure ventilation (NIPPV) is provided via a nasal mask or face mask. Invasive positive pressure ventilation is performed via endotracheal intubation or tracheostomy.

16.5.3.2 Noninvasive Positive Pressure Ventilation

NIPPV should be used in patients when conventional methods of oxygen therapy (nasal cannula and mask) cannot maintain satisfactory oxygenation, when the patient exhibits use of auxiliary respiratory muscles or has severe respiratory difficulties, or when the patient has deteriorated oxygenation disorder. However, patients must have a good state of consciousness, the ability to expectorate sputum, adequate breathing ability, good hemodynamic conditions, and be amenable to NIPPV (Zhang and Gao 2006; Critical Care Medicine Branch of the Chinese Medical Association 2007; Yu 2008).

NIPPV is contraindicated when patient exhibits decreased consciousness, weak or intermittent breathing, weak expectoration, severe organ dysfunction (upper gastrointestinal bleeding or hemodynamic instability), pneumothorax or mediastinal emphysema without drainage, severe bloating, or in cases of upper airway or maxillofacial injury, surgery, or deformity. NIPPV is not recommended when the patient is not cooperative or experiences mask discomfort.

Randomized controlled clinical trials have shown that early application of NIPPV in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), acute cardiogenic pulmonary edema (ACPE), or immunosuppression can reduce the need for endotracheal intubation and lower hospital mortality rates (Critical Care Medicine Branch of the Chinese Medical Association 2007). In cases of pulmonary TB with respiratory failure, both Chinese and international studies indicate that early application of NIPPV or mechanical ventilation as a sequential treatment can benefit patients (Agarwal et al. 2005; Deng and Guo 2005; Zhu 2006; Men et al. 2009; Zhou 2010). However, the specific effects need to be confirmed through randomized controlled clinical studies.

The two most common types of NIPPV are continuous positive airway pressure (CPAP) ventilation and bi-level positive airway pressure (BiPAP) ventilation. BiPAP has two modes: S mode and T mode. The S mode is for spontaneous breathing ventilation and is the equivalent of pressure support ventilation (PSV) and PEEP. The T

Table 16.6 BiPAP parameters (Yu 2008)

Parameters	Reference value
IPAP/tidal volume	10–25 cmH_2O/7–15 mL/kg
EPAP	3–5 cmH_2O (Type I respiratory failure with a 4–12 cmH_2O)
Back-up frequency (T mode)	10–20 times/min
Inspiratory time	0.8–1.2 s

mode is for back-up control ventilation and is the equivalent of pressure controlled ventilation (PCV) and PEEP. The BiPAP parameters include inspiratory pressure (IPAP), expiratory pressure (EPAP), and back-up control of ventilation frequency. When the spontaneous breathing interval is below the set value (determined by the back-up frequency), the ventilator is in S mode; when the self-breathing interval exceeds the set value, the ventilator automatically switches to T mode.

CPAP is preferred for use in cases of acute cardiogenic pulmonary edema; however, BiPAP may be considered for use in cases of hypercapnia or in patients who have continued difficulty breathing.

In principle, BiPAP parameter adjustments (IPAP and EPAP) are started from a lower level and then gradually increase until a satisfactory level of ventilation and oxygenation is reached, or until the ventilation has reached the highest level the patient can tolerate. The common reference values for BiPAP ventilation parameters are shown in Table 16.6 (Zhang and Gao 2006; Critical Care Medicine Branch of the Chinese Medical Association 2007; Yu 2008).

If the application of NIPPV does not improve the patient's condition within 1–2 h, invasive ventilation should be used.

16.5.3.3 The Basic Model and Parameters Setting of Mechanical Ventilation

Assist-Control ventilation (ACV) is combination of two kinds of ventilation, assisted ventilation (AV) and controlled ventilation (CV). When the patient's inspiratory force is able to trigger the breathing machine and the ventilation rate is higher than any preset frequency, the machine is operating in AV mode. When the frequency of spontaneous breathing is lower than the preset frequency, or there is an inability to trigger the ventilator through breathing, the ventilator switches to CV mode and gives positive pressure ventilation corresponding to the preset tidal volume and frequency. A-C mechanical ventilation is commonly used in ICU patients. This provides basic synchronized ventilation with spontaneous breathing, and ensures minimum minute ventilation in patients with breathing instability (Zhang and Gao 2006; Critical Care Medicine Branch of the Chinese Medical Association 2007; Yu 2008).

The A-C capacity switch for ACV ventilation has the following parameters: trigger sensitivity, tidal volume, respiratory rate, inspiratory flow/flow waveforms. The A-C pressure switch parameters are trigger sensitivity, pressure level, inspiratory time, and respiratory rate.

Synchronized intermittent mandatory ventilation (SIMV) is a combination of spontaneous breathing and controlled ventilation breathing. The synchronous instruction of positive pressure ventilation can be triggered by patient's spontaneous breathing. Between two instructed ventilation cycles, patients could breath spontaneously. Instructed breathing can be proceeded in the form of prebreathing capacity (capacity-controlled SIMV) or pre-pressure (pressure-controlled SIMV). SIMV can cooperate with a patients' spontaneous breathing and reduce the patients' struggle with the ventilator. The level of respiratory support can be changed by changing IMV frequency from full support to partial support. SIMV can be used during the ventilator weaning process for patients who have been on a ventilator for a long time. The parameters for SIMV are tidal volume, flow rate/inspiratory time, controlled frequency, and trigger sensitivity. The pressure level and inspiratory time should be set when SIMV is controlled by pressure.

Pressure support ventilation (PSV) is one of the ventilation support modes in which the patient triggers ventilation and controls the respiratory rate and tidal volume. It switches from inspiratory to expiratory phase when the airway pressure reaches the preset pressure level and inspiratory flow decreases to below the threshold level. If the ventilator is set to the appropriate level, it can effectively reduce the work of breathing and have a positive impact on hemodynamics. Some studies suggest that 5–8 cmH_2O of PSV can overcome the circuit resistance of endotracheal intubation and ventilator, so PSV can be used in the ventilator weaning process. The parameters for PSV are pressure, trigger sensitivity, pressure rise rate, and, in some ventilators, expiratory sensitivity.

Continuous positive airway pressure (CPAP), as previously discussed, assists patients in breathing on their own. The ventilator maintains airway pressure within the entire respiratory cycle (inspiratory and expiratory period). CPAP has all the advantages of PEEP, such as increasing the alveolar pressure and functional residual capacity, increasing oxygenation, preventing airway and alveolar collapse, improving lung compliance, and reducing the work of breathing against $PEEP_i$. However, CPAP pressure that is too high can increase peak pressure and mean pressure of the airway, reduce venous return volume, and reduce blood perfusion of important organs such as the liver and kidneys. In addition, spontaneous breathing produces a slightly lower mean intrathoracic pressure than the same PEEP when CPAP is used. The only CPAP parameter is pressure. *Biphasic positive airway pressure (BIPAP)* gives two different alternating levels of positive airway pressure during spontaneous breathing. It switches between the low pressure and high pressure regularly, and its high-pressure time, low-pressure time, high pressure level, and low pressure level are independent and variable. Functional residual capacity (FRC) reduction, which is produced by switching from high pressure level to low pressure level, can increase expiration volume and improve alveolar ventilation. The BIPAP parameters are high pressure level (*P* high), low pressure level (*P* low), high-pressure time (*T* insp), respiratory frequency, and trigger sensitivity.

The Main Parameters of Mechanical Ventilation

Tidal volume settings in volume-controlled ventilation mode are usually determined based on body weight (5–12 mL/kg) combined with the respiratory system compliance and resistance adjustment. Avoid platform airway pressure exceeding 30–35 cmH_2O. In pressure-controlled ventilation mode, the tidal volume is depended on preset pressure, respiratory system resistance, and compliance, and should eventually be adjusted according to blood gas analysis.

Respiratory rate settings are usually 12–20 breaths/min in adults. In individuals with acute/chronic restrictive lung disease, the setting may be more than 20 breaths/min based on minute ventilation and the PCO_2 level of the target. However, an excessive respiratory rate can lead to increased air trapping and an elevated $PEEP_i$ and should be avoided.

Flow rate for an adult is commonly set between 40 and 60 L/min and adjusted according to minute ventilation, respiratory system resistance, and lung compliance. The ideal peak flow should meet the patient's peak inspiratory flow rate. The velocity waveform commonly used in the clinic is slow wave or square wave. In the pressure-controlled ventilation mode, flow rate is determined by the selected pressure level, airway resistance, and the patient's inspiratory effort.

The *inspiratory time* in spontaneously breathing patients is usually set at 0.8–1.2 s, or a *respiratory ratio* of 1:1.5–1:2. Controlled ventilation patients may have extended inspiratory times and respiratory ratios so as to elevate mean airway pressure and improve oxygenation, but close attention should be paid to $PEEP_i$, patient comfort, and the effects on the cardiovascular system.

Trigger sensitivity under normal circumstances is set with the pressure trigger at −0.5 to 1.5 cmH_2O and the flow trigger at 2–5 L/min. The proper trigger sensitivity settings will make the patient more comfortable and promote human–machine coordination.

Inspired oxygen concentration (FiO2) can be set high (100 %) in the initial phase of mechanical ventilation to quickly correct severe hypoxia, and later adjusted based on target PaO_2, PEEP levels, MAP levels, and hemodynamic status as appropriate. FiO_2 should then be reduced to 50 % or less. If SaO_2 cannot be maintained >90 %, then PEEP should be added to increase mean airway pressure and sedatives or muscle relaxants should be administered. If appropriate, PEEP and MAP may be adjusted as needed to increase $SaO_2 > 90$ % and maintain a minimum FiO_2.

Proper *PEEP settings* will recruit collapsed alveoli, increase mean airway pressure, improve oxygenation and reduce venous return, decrease left ventricular afterload, and reduce the work of breathing caused by $PEEP_i$. PEEP is often used in ARDS as the representative of the type I respiratory failure. When setting PEEP, refer to target PaO_2 and oxygen delivery and consider FiO_2 and tidal volume.

Lung Protective Ventilation Strategy

In order to avoid ventilator-associated lung injury in cases of pulmonary TB with bullae or lung damage, a lung protective ventilation strategy should be designed to avoid excessive inspiratory plateau pressure and tidal volume. The lung protective

ventilation strategy should have a low tidal volume (6 mL/kg), an appropriate level of PEEP, end-inspiratory platform maintained at 30 cmH_2O, and a $PaO_2 > 58–60$ mmHg or oxygen saturation > 90 %. Limiting oxygen concentrations to less than 60 % avoids oxygen toxicity (Zhang et al. 2002; Du et al. 2003).

16.5.4 Supportive Treatment

Supportive treatment includes nutritional support, antishock therapy, and maintenance of the balance of pH, water, and electrolytes. All of these supportive treatments are needed for protein synthesis, for organ function, and to sustain life, especially in patients with critical TB.

16.5.4.1 Nutritional Support

TB is a chronic wasting disease. Critical TB is associated with secondary infections, fever, hypoxemia, and increased work required for breathing. These factors increase the risk of malnutrition. More than half of TB patients have hemoglobin < 9 g/dL, 92.5 % have severe anemia, and 67.2 % have hypoproteinemia (Silva et al. 2010). Malnutrition lowers patient serum total protein and albumin, reduces lesion repair function, damages immune function, and decreases the number and function of lymphocytes in the cellular immune system. Malnutrition delays healing, and this delay increases the chances of transmission. Moreover, malnutrition hypoalbuminemia interferes with anti-TB drug delivery and changes the effective concentration of anti-TB drugs, altering their efficacy (Paton et al. 2004). Nutritional support should be given to severe TB patients as soon as possible. The first choice is enteral nutrition therapy; however, adequate measures must be taken to avoid the occurrence of regurgitation and aspiration. It may be necessary to add a gastrointestinal prokinetic drug. Overfeeding should be avoided in patients with respiratory failure. This is especially true with carbohydrate supplements, which increase carbon dioxide production, increase the respiratory quotient, and increase respiratory load. Patients with intestinal TB complicated by obstruction, fistula, and severe abdominal infection cannot tolerate enteral nutrition, so adequate parenteral nutrition will be necessary (Heyland et al. 2003; Jiang 2008).

16.5.4.2 Antishock Therapy

Hemoptysis, septic shock, and low blood pressure after mechanical ventilation require rapid fluid resuscitation to ensure the effective perfusion of oxygen and blood into the tissues and organs. Vasoactive drugs can be administered in combination with hemodynamic monitoring. Obstructive shock caused by tuberculous pericarditis, pericardial tamponade, or tension pneumothorax requires pericardiocentesis or thoracic drainage to relieve obstructive lesions as soon as possible.

Critical TB, despite being an infrequent cause of multiple organ failure, still has a relatively high mortality rate. There should be a prompt and aggressive diagnostic strategy to identify patients with more than one organ failure and instable hemodynamics who require mechanical ventilation and ICU care. Therefore, specialized TB intensive care units should be set up in high incidence areas. Sufficient medical personnel and equipment should be provided to ensure treatment to reduce TB transmission and patient mortality.

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Chapter 17
New Diagnostic Tools for Early Detection of TB

Yanlin Zhao and Shengfen Wang

17.1 Introduction

Early, effective diagnosis, especially for smear-negative pulmonary tuberculosis (TB) and multidrug-resistant tuberculosis (MDR-TB), is a key element of global TB control. Although global TB control initiatives have prevented nearly six million people from dying of TB over the past 15 years (Lonnroth et al. 2010), studies have shown that a majority of the patients who receive treatment for TB have already infected others in the community (Dye and Williams 2010). The long-term elimination of TB requires a continued amplification of early diagnosis and treatment, intensified case detection, and an emphasis put on prevention, including preventive therapy (Lonnroth et al. 2010).

MDR-TB and coinfection with HIV are serious obstacles to global TB control. This is primarily due to the limited availability of clinical resources for diagnosing TB in high burden areas of the world and the complexity of MDR-TB diagnosis. Presently, there is no reliable and rapid way for HIV–TB coinfected patients to get a timely, accurate diagnosis. If MDR-TB and extremely drug-resistant tuberculosis (XDR-TB) cannot be effectively controlled, the goal of controlling TB in developing countries will be seriously challenged (Zhao et al. 2009, 2012). In order to effectively reduce the spread of TB and to lower the lethality of MDR-TB, XDR-TB, and HIV–TB coinfection, a rapid and reliable diagnostic method is urgently needed. None of the current diagnostics meet the need for a simple, rapid, and inexpensive method.

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Diagnosis of TB requires laboratory identification of acid fast bacilli (AFB) by smear microscopy, and/or *Mycobacterium tuberculosis* solid culture. Liquid culture methods are currently considered the gold standards for isolating mycobacteria by using of liquid media. New technologies for molecular diagnosis of TB, such as molecular diagnostics line probe assay, allow rapid detection of *M. tuberculosis* molecular biomarkers as well as genes related to rifampicin (RIF) and isoniazid (INH) resistance. Although liquid culture and the Line Probe Assay have been recognized and recommended by the World Health Organization (WHO), their complexity and cost, and the fact that they require controlled laboratory settings, limit the application of these methods in resource-restricted countries (WHO 2006).

It was thought that PCR technology, developed in the 1980s, would have a more significant impact on the clinical diagnosis of TB. Molecular typing diagnostic methods have many advantages in the treatment, regulation, and monitoring of DR-TB. These standardized laboratory methods are rapid, have the potential for high throughput, and require less demanding laboratory biosecurity. Despite these theoretical advantages, however, widespread application of these techniques has been limited because of the complexity of extracting and detecting DNA from sputum specimens and the rigorous safety requirements for handling *M. tuberculosis* samples. Nucleic acid amplification tests (NAATs) have been used for many years. Current NAATs have high specificity, but modest and variable sensitivity, especially for smear-negative and extrapulmonary TB (Pai et al. 2003; Greco et al. 2006). At present, diagnosis of TB in most laboratories of China relies on traditional methods. The traditional drug susceptibility test (DST) requires cultivation of *M. tuberculosis*, so the combination of the traditional culture method and DST requires an investment in laboratory biosecurity, infrastructure, and human resources. Therefore, the application and dissemination of traditional diagnostic methods and more recent molecular typing methods has been slow.

Since Koch identified *M. tuberculosis* as the cause of TB in 1882, new diagnostic techniques and treatments have attempted to keep pace with the spread of TB. However, TB remains a serious infectious disease that threatens people's lives, and its control will require a continuous and comprehensive effort over many years. The emergence of drug-resistant TB and HIV/AIDS has made the diagnosis and treatment of TB more complex. In this chapter, we will describe the current state of TB diagnostic techniques, the associated laboratory requirements, and strategies for developing new diagnostic methods.

17.2 The Current State of Clinical Diagnosis of TB

17.2.1 Diagnosis of TB in Developed Countries

Conventional sputum smear microscopy, culture isolation, and drug sensitivity testing still play important roles in TB diagnosis in most developed countries. At the same time, some rapid diagnostic techniques like the rapid mycobacterial liquid

culture-screening method, nucleic acid hybridization test, 16 s DNA sequencing, HPLC analysis of cell wall lipids (mycolic acid), nucleic acid amplification, fluorescence in situ hybridization (FISH), and phage FASTPlaque have all contributed to gradually reducing the time for a diagnostic report to 2 days (Lonnroth et al. 2010; Dye and Williams 2010; Zhao et al. 2009, 2012).

In recent years, many developed countries have adopted the use of IFN-γ release assays (IGRAs), even though the cutoff values can vary significantly by country (WHO 2006, 2010). IGRAs aid in the diagnosis of TB by measuring the antigen-specific release of IFN-gamma from the T cells of infected individuals. Some studies have shown that IGRAs such as QuantiFERON-TB® and T-SPOT.TB® have higher specificity than the tuberculin skin test (TST) in countries where Bacillus Calmette–Guerin (BCG) vaccination is mandatory. This is because IGRAs, unlike TST, use antigen stimulators (ESAT-6 and CFP-10) that are not present in the BCG vaccine (Hansted et al. 2009; Dheda et al. 2009).

In developed countries, genotyping technology is widely used. This technique can be used to track the transmission of mycobacteria via genotype analysis. It is useful in routine contact investigations, can be used to identify false positive culture results, and aids in the early detection of TB outbreaks. The list of genotyping methods includes restriction fragment length polymorphism (IS6110-RFLP), variable number of tandem repeats (VNTR), mycobacteria interspersed repetitive units (MIRU), spacer oligonucleotide typing (spoligotyping), single-nucleotide polymorphisms (SNPs), long segment polymorphism (LSP), and deletion mapping. Although IS6110-RFLP is a low-throughput method that requires the cultivation of large numbers of bacteria, making large-scaled genotyping difficult, the IS6110-RFLP technology is still the gold standard for genotyping *M. tuberculosis* (van Embden et al. 1993). There are plenty of advanced techniques for genotyping *M. tuberculosis*; the difficulty lies in the interpretation of the test results.

17.2.2 Experimental Diagnostics in Developing Countries

Of the 22 high burden TB countries listed by the WHO, 21 are developing countries. Where resources are limited, sputum smear microscopy and culture confirmation—diagnostic methods that have been used for over one hundred years—are still the primary methods for diagnosing TB in developing countries. Although sputum smear microscopy has low sensitivity in HIV endemic areas, its convenience, low cost, and ability to identify infectious TB cases (active TB) has led the WHO to recommend it as the primary diagnostic method for TB detection in developing countries. There are a limited number of laboratories in the developing world that can carry out culture confirmation and drug susceptibility testing. New diagnostic technologies have been well established, but their high cost and requirement for a high level of expertise limit their application.

17.3 Urgent Need for New TB Diagnostics

17.3.1 The Limitation of Traditional TB Diagnosis and the Necessity of Introducing New Diagnostic Technologies

Traditional diagnosis of TB is relatively simple and inexpensive, but there are obvious limitations associated with it. Sputum smear microscopy is the most basic TB test in the laboratory and can provide a preliminary diagnosis for physicians, but low sensitivity and specificity limit its usefulness. An increase in the number of smear-negative TB patients in areas with a high prevalence of HIV/AIDS further highlights the limitations of this method. Culture confirmation of *M. tuberculosis* is still the gold standard for TB diagnosis, and conventional drug sensitivity testing which requires growth on solid media is still widely used in many parts of the world. However, these techniques are time-consuming and take up to several weeks even in best-case scenarios. At present, treatment delay and misdiagnosis caused by traditional TB diagnostic techniques are common, and the lack of a fast and accurate method for diagnosing TB is the main obstacle in TB control.

Although progress has been made in the detection and treatment of TB globally, we are still facing many challenges including TB and HIV coinfections, DR-TB, and TB among migrants. Laboratory testing will play an increasingly important role in TB control and the traditional bacteriological tests are no longer sufficient to meet the needs of modern TB control.

17.3.2 High Priority Issues in Diagnosis

17.3.2.1 Identification of TB Cases

In developing countries, the identification of TB patients relies mainly on sputum smear microscopy and radiological imaging. These methods are simple and low cost but have low sensitivity and are labor intensive. It is very difficult to accurately diagnose patients who are in the initial stages of TB infection using these methods. By the time an accurate diagnosis can be made, patients may have lost the opportunity for early treatment and the infection may have been transmitted to others. In addition, smear-negative TB, extrapulmonary TB, and TB among children are difficult to diagnose and require methods and tools with higher sensitivity and specificity.

17.3.2.2 The Identification of Mycobacterium Species

M. tuberculosis can be divided into three types: *Mycobacterium tuberculosis* complex (MTC), nontuberculous mycobacteria (NTM), and *Mycobacterium leprae*. MTC is responsible for human TB infections (Al-Attiyah and Mustafa 2008). There

are a great many NTM widely distributed in the environment. They can be pathogens or conditional pathogens. In recent years, increasing attention has been given to the pathogenicity of NTM, which often infects immune-suppressed or immune-deficient patients (Buijtels et al. 2010; Bonard et al. 2004). It is a common opportunistic infection in AIDS patients. The diseases caused by *M. tuberculosis* and NTM have similar clinical manifestations but different sensitivities to various drugs. In addition, the drug sensitivities of different types of NTM vary widely, as do their clinical treatments and epidemiological consequences. Therefore, identifying the infecting species of mycobacterium is important for appropriate treatment of the patient. Established methods for identifying mycobacterium species are based on cellular morphology, growth rate, chromogenesis, and biochemical testing. Since these methods are time-consuming and have limited accuracy, rapid clinical mycobacterial identification methods are needed.

17.3.2.3 Rapid Drug Sensitivity Testing

At present, drug sensitivity testing (DST) of *M. tuberculosis* in many developing countries takes at least 8–12 weeks if solid medium is used and 4–8 weeks if liquid medium is used. Since test results may not be known for weeks, patients may receive inappropriate anti-TB drug therapy in the meantime. This may allow the development of resistance to drugs that have wide application in treating other strains of *M. tuberculosis* and increase the risk of transmitting the resistant strain. In order to ensure patients get proper treatment and reduce the generation and transmission of resistant strains of *M. tuberculosis*, rapid drug sensitivity testing is urgently needed.

17.4 Screening Procedures, Evaluation Strategies, and Mechanisms for Developing New TB Diagnostics

China has a large and complex TB laboratory network within its TB control and medical care systems. Laboratories at county level are responsible for case finding and management of TB patients. Provincial-level TB laboratories are responsible for training technicians and performing quality control of county level. The national TB laboratory is in charge of equipping and maintaining laboratory networks and quality control. Different levels of laboratories face different challenges. Strengthening TB laboratory services is one of the best means for overall improvement of laboratories. New techniques introduced must be used in appropriate laboratory services and must be suitable for different levels of laboratory services, so procedures for the screening and evaluation of new diagnostic technologies should be established.

17.4.1 Selecting Diagnostics Based on Need

Within China's national TB control system, different types of diagnostic laboratories face different challenges. The appropriate diagnostic techniques and methods selected for each laboratory should be based on the patient populations served and its testing needs as well as the required facilities, equipment, human resources, technological know-how, and levels of biosafety protection.

District-level (local) institutions for the prevention and treatment of TB are the most basic unit of a national TB control system. They are responsible for finding, treating, managing, and tracking TB patients. Diagnosis relies primarily on radiographic examination and sputum smear microscopy. Clinicians determine the treatment regimen based on a medical exam, a medical history, and a treatment history obtained through a patient interview. The level of protection for clinicians at the district level is generally substandard because of inadequate equipment, staffing, and facilities. They often have only one room for Ziehl–Neelsen smear examination. Few labs have biosafety cabinets and thus use fume hoods instead. Most of the fume hoods have no filtration devices, and *M. tuberculosis* may spread from the lab and pollute the environment. Some labs have insufficient technical expertise due to high staff turnover, leaving few workers to do the job of several. Often, the quality of sputum smear microscopy cannot be ensured due to heavy workloads and time constraints, and most clinics at the local level are unable to perform drug sensitivity testing. These clinics would benefit from the best new method for rapid identification of *M. tuberculosis* in sputum specimens from suspected TB patients.

County-level organizations for TB prevention and treatment, particularly specialty TB hospitals and municipal hospitals for infectious diseases, play crucial roles in TB diagnosis and treatment. Patients are often admitted to municipal hospitals when previous anti-TB drug therapy proves ineffective, meaning that a high percentage of these patients may be infected with drug-resistant TB. In the majority of municipal hospitals, the diagnosis of TB relies on traditional methods, such as sputum smear and mycobacterial culture. Drug sensitivity testing is time-consuming, and often physicians do not have information regarding resistance before determining the treatment regimen. This often leads to inappropriate treatment and may lead to the generation and transmission of new drug-resistant strains of TB. Generally speaking, municipal TB clinics and hospitals have better conditions and equipment than district-level clinics. They often have specialized housing for TB detection, biological safety cabinets, and personnel with a relatively high level of expertise. The challenge that municipal institutions face is to identify the infecting strain of mycobacterium and its drug sensitivity quickly enough to guide the clinicians' initial treatment, and thereby stem the emergence and spread of drug-resistant strains of TB.

By the time most patients visit provincial-level TB control institutions and hospitals they are usually already undergoing treatment with anti-TB drugs. Many of these patients are immuno compromised, elderly, have medical complications, or have complicated treatment histories. They often need more personalized treatment, and physicians need test results related to strain identification and drug susceptibility quickly to form the basis for developing a treatment plan. Though they have the

strongest need for rapid results, few provincial hospitals have adopted the liquid culture method for strain identification and susceptibility testing. Most still use the more time-consuming traditional solid culture method, which does not advance effective clinical diagnosis and treatment.

17.4.2 Assessment Strategies for New Diagnostic Methods

In order to introduce new diagnostic techniques, the executive leadership of China's national health system must make an overall assessment of the current status of prevention and control systems to determine if the implementation of a new technique is supported by current policies and the regulatory environment. The introduction of new diagnostic methods will inevitably lead to changes in management and treatment of TB patients. It is important to consider how to transition from old to new regulations and whether such changes can win the approval of doctors, patients, and institutions at all levels of TB control. Moreover, the government needs to conduct comprehensive analysis of the new diagnostic techniques, provide sufficient funding for their implementation and promotion, and support the required scaling of infrastructure, equipment, and human resources.

Individual TB control institutions must be assessed based on their needs, responsibilities, and challenges. Past applications and implementations of technology at an institution should also be considered. To choose the proper techniques from many available options, careful consideration needs to be given to the accuracy, reliability, safety, affordability, and maintenance of material and equipment at the given institution. Another factor that is often overlooked is that the medical staff must accept the new technology for its successful adoption.

Often, new diagnostic products are approved but lack extensive field assessment at the sites of likely implementation. Problems related to the integration of new techniques with traditional methods are likely to arise. Therefore, on-site evaluation programs must be developed to assess the implementation of new methods. Such evaluation and research can help to identify specific on-site problems related to new procedures, tests, or protocols. For instance, when applying the new techniques it may be necessary to modify existing infrastructure, adjust funding and staffing, or provide additional training. If shared, the field assessments and evaluations of new techniques can serve as important references for other healthcare administration departments.

17.4.3 Guidelines for the Selection, Assessment, and Promotion of New TB Diagnostic Techniques

The traditional method of solid media culture requires 4–8 weeks to complete, and in some remote areas the cultivation of *M. tuberculosis* cannot be performed. Furthermore, although direct sputum smear microscopy is quick and easy to

implement in the most basic of laboratories, it has very low sensitivity. As a response to the shortcomings of these traditional techniques, new molecular biology-based diagnostic techniques have been developed in recent years through joint efforts between governmental and nongovernmental organizations.

In the book "Pathways to Better Diagnostics for Tuberculosis" by the Stop TB Partnership, the key steps in developing a new TB diagnostic are: assess the need, develop a concept with proof of principle, optimize the prototype, and evaluate the test's accuracy and reliability in a population where the test is clinically indicated (WHO 2010). If significant test results are obtained, the test may then be introduced at specific and limited testing sites (such as medical agencies or project sites) for application and impact assessment. Data from the evaluation, application, and impact assessment of the product will serve as a major reference for governmental decision-making regarding the formation and revision of guidelines for TB diagnosis. In practice, these steps can be conducted in cycles rather than being done in a linear manner.

17.4.3.1 Guidelines for Screening, Evaluation, and Implementation of New Diagnostics

The purpose of these guidelines is to regulate the use of new TB diagnostic techniques in China, provide a basis for the central and local health administration's decision-making, guide national TB prevention efforts, and develop mechanisms for the selection, evaluation, and implementation of new TB diagnostic techniques (Ou and Zhao 2011).

The process of selecting and evaluating new diagnostic TB techniques must follow the principles of fairness, justice, transparency, and scientific objectivity when selecting new TB diagnostic techniques from home and abroad.

17.4.3.2 Mechanism for Selecting, Evaluating, and Promoting New Diagnostic Techniques for TB

Selection of new diagnostic techniques should be initiated and organized by the National Tuberculosis Reference Laboratory and the results should be presented to expert groups from TB laboratories.

17.4.3.3 Selection Principles

Selection of new diagnostic methods should be based on the diagnostic purpose of the new technique and the needs of different laboratory levels in the country. Priority should be given to new techniques that can improve the detection of smear-negative TB, extrapulmonary TB, and TB in children, and also preference should be given to

methods that are simple, accurate, safe, fast, cheap, and easy to perform in the laboratory at the grassroots level with test results being available within 24 h. The techniques that can rapidly identify *M. tuberculosis* and detect susceptibility to first- and second-line anti-TB drugs as well as monitor the efficacy of TB treatment should be selected. Establishing and optimizing laboratory networks is a challenge, and new techniques must be introduced at the appropriate laboratory levels. New diagnostic techniques should be divided into categories (based on utility, biosafety, expertise, and requirement for new equipment) corresponding to TB control institutions at the national, provincial, county, and local level, as well as to comprehensive hospitals and TB-specific hospitals. Laboratories at higher levels may implement technology used in the lower level laboratories. China is a high TB burden country with nearly 45 % of people infected with TB. Techniques that can distinguish between active TB and latent TB should be selected in order to provide the basis for the rational use of TB prevention and treatment measures. Meanwhile, different types of patient samples to be tested, such as nucleic acid, whole blood, tissue, serum, and pure cultures, should be taken into consideration.

Within a predetermined time frame, the National Tuberculosis Reference Laboratory may select the test or tests to be evaluated and promoted from a group of available techniques designed to test the same type of samples, at the same laboratory level, for the same diagnostic purpose.

17.4.3.4 The Role of the National Tuberculosis Reference Laboratory in the Evaluation and Selection of New Diagnostic Techniques in China

As new TB diagnostic methods are emerging rapidly, new TB technology methods are regularly assessed and endorsed by the WHO. The National Tuberculosis Reference Laboratory may obtain information from the WHO or other countries regarding new TB laboratory diagnostic techniques through literature searches, expert advice, and from developers of new technology in diagnostic laboratories. Detailed information of the new diagnostic technologies is collected by the National Tuberculosis Reference Laboratory, including registration information for new technology, place of origin, intended use, principles of detection, method of detection, equipment required, reagent storage conditions, targets to be detected, scalability, internal quality control, sensitivity, compliance rate, and repeatability. According to the requirements of different levels of laboratory testing in China TB laboratory network, the National Tuberculosis Reference Laboratory selects promising technologies and validates these methods by testing 100–600 known and unknown samples. A group of TB experts then review the initial data on reliability, safety, and cost-effectiveness of the new technique. Based on the current situation and the needs of domestic TB laboratories in China, the most promising test or tests are selected by the TB experts group for further clinical evaluation.

17.5 Evaluation of New Diagnostic Technologies

The main purpose of the assessment phase is to evaluate the accuracy, reliability, and effectiveness or efficacy of new TB diagnostic technologies in two phases: small-scale and large-scale. In order to formulate evaluation strategies, The National Tuberculosis Reference Laboratory should seek advice from the advisory board of the Ministry of Health, medical experts, TB control program experts, and experts from the National TB Laboratory and the Disease Control Department. At the same time, an evaluation of strategies should be conducted by bringing together TB prevention agencies at the provincial, county, and district levels, as well as in TB-specific hospitals or general hospitals, where the new technology is to be applied (Fig. 17.1).

During the assessment phase it is necessary to determine the goals of the evaluation, the target population for which the new technology is intended, and the details of implementing the standardized assessment. Establishing these goals may reduce the influence of the developers of the new technology, who may have potential conflicts of interest.

17.5.1 Content of Evaluation

The performance of the selected new TB diagnostic methods are assessed by determining its sensitivity and positive predictive value (including confidence intervals) by testing sputum- and culture-positive TB patients, and specificity and negative predictive value (including confidence intervals) by testing sputum- and culture-negative individuals suspected of having TB. An assessment of the reliability of new diagnostic techniques includes the following sections or parameters: type of study design (cross-sectional studies or case-control studies, prospective or retrospective studies), project sites and types of specimen tested (patient and specimen flow), sample size (the number of patients and controls, the number of specimens), study inclusion and exclusion criteria (including age, sex, severity of disease, and complications such as HIV infections), choice of cutoff point (gold standard) for diagnosis, blind test and results of gold standard, test site (including a list of responsibilities and roles of collaborators and researchers), ethical considerations and informed consent, importing laboratory materials and other lab management considerations, data management and analysis (statistical methods), research budget, and schedule and delivery.

17.5.1.1 Cost-Effectiveness Assessment

Cost–benefit analysis is mainly used for comparing the costs and benefits of new diagnostic techniques and similar products. Cost-effective does not mean the lowest cost—rather, it means maximizing the benefits and health effects at the lowest possible cost. Costs should be calculated from the perspective of the providers of the technology and the TB patients. For the providers, cost includes laboratory-related

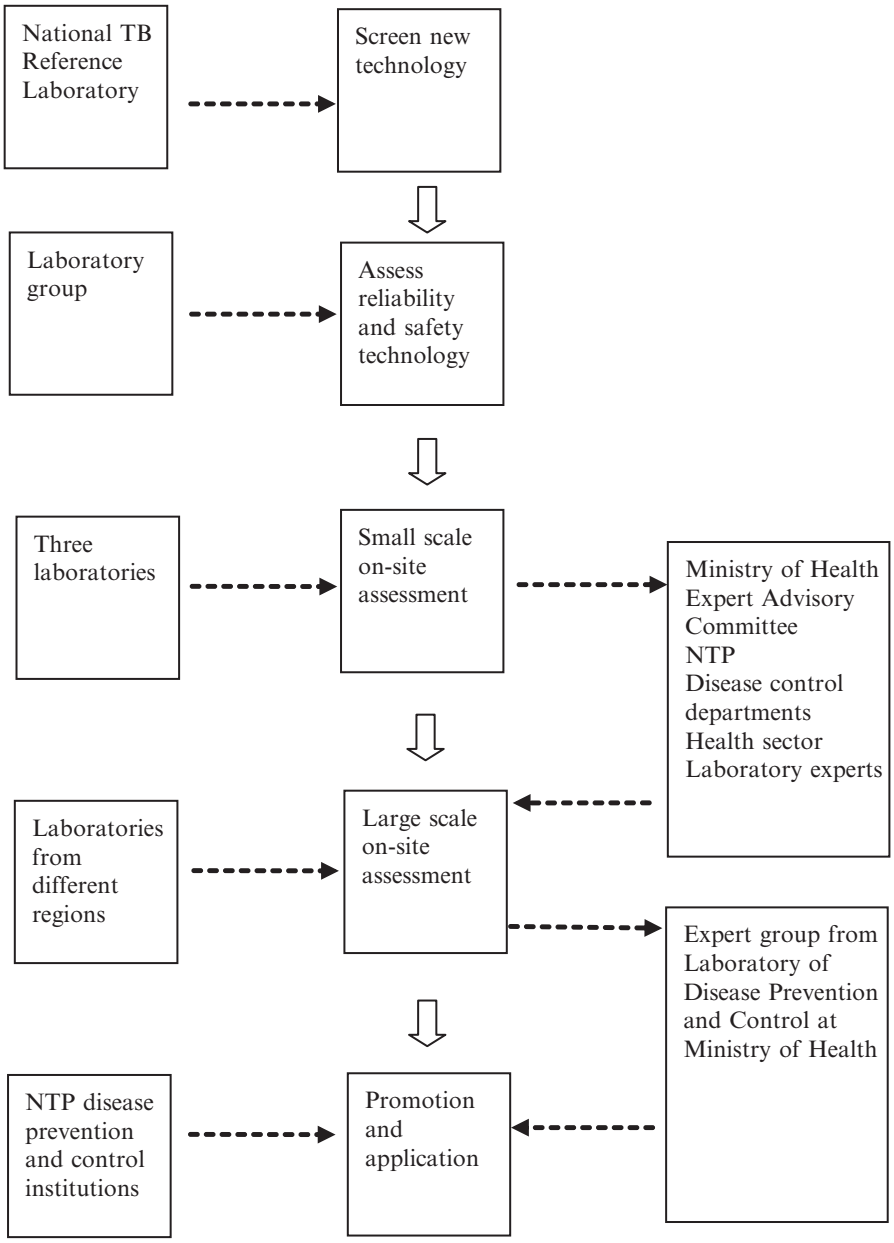

Fig. 17.1 Mechanism for the selection, evaluation, promotion, and application of new diagnostic techniques for the National TB Control Program (NTP)

direct cost and cost associated with other types of diagnostic and medical services. For patients, cost includes direct medical cost as well as time loss for both patients (due to illness) and their families (due to patient care). The benefits of a new technology should include increased sensitivity and specificity, a reduction in time to diagnosis, improved case outcomes, and a reduction in disease transmission.

17.5.2 Assessment Process

The goal of the assessment is to collect primary data related to the feasibility, reliability, acceptability, repeatability, controllability, and cost-effectiveness of the new technique in the field. Usually, the National Tuberculosis Reference Laboratory selects three laboratories to conduct a small-scale clinical validation with a sample size of 1000. Assuming the small-scale results are promising, the National Tuberculosis Reference Laboratory will determine if a large-scale evaluation is needed with the input and guidance of the Advisory Board of the Ministry of Health and the Disease Control and Health Care Departments, and should refer to the technology's registration information from the State Food and Drug Administration. For new technologies that are selected for large-scale evaluation, the National Tuberculosis Reference Laboratory will conduct the large-scale clinical evaluation of the new technology in all districts within two qualified cities, or in six municipal laboratories from the eastern, central, and western areas of the city. A quality assurance system of evaluation is to be established during the assessment process.

17.5.3 Guidelines for Data Collection, Analysis, Reporting, and Feedback from the Evaluation

During new technology methods assessment, all the laboratories involved in evaluation must keep a copy of all the original records on file. Participating laboratories perform data collection and report the results to the National Tuberculosis Reference Laboratory, which collects all the data and performs the analysis. Results of the evaluation of the new TB diagnostic methods will then be published officially.

17.6 Promotion

The decision of whether to adopt the new technology and how to establish a model for its promotion should be based on the evaluation results, as well as discussion among the Advisory Board of the Ministry of Health, experts in national TB control and management, and experts from disease control departments, health departments, and TB laboratories. Once selected, the new diagnostic technology should be

incorporated into national TB control programs in order to standardize training, supervision, and quality control.

The promotion of new TB diagnostics should be divided into two stages: pilot promotion in selected areas followed by national promotion. The initial promotion should be conducted at a number of TB control institutions from different regions with use of both traditional diagnostic methods and concurrent application of new techniques. Clinicians will then make diagnoses and design treatments based on the combined results. Once experience has been accumulated in the demonstration areas, the diagnostic technology should enter the national stage of promotion in the appropriate laboratories. The combination of new and traditional diagnostic techniques should continue to be used for a certain period of time to diagnose suspected TB patients.

17.7 Currently Available New Diagnostic Methods

TB diagnostics are changing rapidly. New TB technology is regularly assessed and recommended by the WHO. At present, WHO-recommended techniques include light-emitting diode fluorescence microscopy (LED-FM), Line Probe Assay, and GeneXpert MTB/RIF detection technology.

17.7.1 Light-Emitting Diode Fluorescence Microscopy (LED-FM)

Most basic level laboratories in China still rely on direct sputum smear examination using the Ziehl–Neelsen (ZN) staining method to detect *M. tuberculosis* and diagnose TB patients. This method is simple, cheap, and easy for technical staff working at the basic level to perform. But an obvious shortfall of this method is its low sensitivity. Fluorescent microscopy (FM) is more sensitive than Ziehl–Neelsen staining microscopy, however, the high cost of traditional fluorescent microscopy has hindered its implementation at the grassroots level. In recent years, LED technology has been applied to optical microscopy to develop LED fluorescence microscopy (LED-FM). LED-FM has higher sensitivity and is suitable to be used in primary laboratories where a heavy sputum smear examination workload exists. Many countries have assessed the feasibility of applying LED-FM at the grassroots level, and the results showed that it could be used in low-income countries in local laboratories where experience using FM was limited (Cuevas et al. 2011; Albert et al. 2013).

The price of an LED fluorescence microscope is similar to that of an ordinary optical microscope and much lower than the price of a traditional fluorescence microscope, and the switch between fluorescence and bright field illumination is extremely simple. Given these advantages, LED-FM may be an improvement over

the current optical microscopy in local TB laboratories. LED-FM has been shown to have higher sensitivity but lower specificity than ZN smear microscopy for diagnosis of pulmonary TB (Cuevas et al. 2011). Laboratory technicians can be trained to use LED-FM, nevertheless, rigorous proficiency testing and intensive quality assurance procedures will be needed during LED-FM implementation. It is therefore necessary to assess the accuracy, reliability, and feasibility of promoting LED-FM at the county level.

17.7.2 Loop-Mediated Isothermal Amplification (LAMP)

Due to the improvement of living standards, health awareness, reduction in the number of smear-positive patients, and increase in the number of smear-negative patients, cultured confirmation often needs to be conducted to aid diagnosis. However, the slow growth of mycobacteria means that culture confirmation cannot meet current clinical needs. Some laboratories with better resources use gene amplification to detect the presence of MTC to support clinical diagnosis. However, gene amplification requires better test facilities, equipment, and personnel training to reduce the risk of cross-contamination. Primary laboratories at the county level often do not have the necessary conditions to support gene amplification; if gene amplification is used for diagnosis, specimens are transported to other laboratories for testing. Therefore, other methods for the rapid diagnosis of TB are needed in county-level laboratories.

Loop-mediated isothermal amplification (LAMP) is a recently developed molecular method that has been successfully implemented in the detection of *M. tuberculosis* in clinical specimens. LAMP has several advantages: the test is rapid, has high sensitivity, is easy to perform, and is cost-effective. LAMP technology does not require expensive thermal cyclers and thus may be appropriate for use at the county level.

17.7.3 Linear Probe Assay

MDR-TB poses a serious challenge to global TB control. Timely diagnosis and appropriate treatment is the key to controlling MDR-TB. The current routine method for testing drug resistance relies on the culturing of *M. tuberculosis*, which requires at least 8–12 weeks on traditional solid media and 4–8 weeks when cultivated in liquid media. Therefore, laboratory susceptibility testing often does not meet the needs for clinical diagnosis and treatment.

Several molecular biology-based methods for rapid TB sensitivity testing have emerged, such as the Linear Probe Assay (LPA). The GenoType MTBDR *plus* test (developed by Hain Lifescience, Nehren, Germany) is a new commercial and easy-to-perform assay developed for the detection of *M. tuberculosis* and any RIF and/or INH

resistance. The test is based on reverse hybridization between the PCR-amplified sample and strips of nitrocellulose-bound probes that include wild-type and mutant genes of interest plus controls. The assay consists of PCR amplification, hybridization of the PCR products to the probe-containing strips, and detection and interpretation of the results. This assay can perform on smear-positive sputum or *M. tuberculosis* culture and give reports within 2 days. LPA has relatively higher sensitivity and specificity and was endorsed by the WHO in 2008. It should be considered for use in provinces and municipalities.

17.7.4 Gene Chip Technology

Gene chip technology (Beijing CapitalBio Technology Corporation, China) can rapidly identify mycobacterial species and identify drug susceptibility to RIF and INH (Guo et al. 2009). This assay system includes a biochip, sample preparation apparatus, hybridization instrument, chip washing machine, and laser confocal scanner equipped with interpretation software for automatic diagnosis. The biochip has now received certification from the China Food and Drug Administration (SFDA) and a CE certificate.

17.7.5 GeneXpert MTB/RIF Detection Technology

GeneXpert MTB/RIF detection technology is simple, fast, has low biosafety requirements, and requires little technical expertise. This method can quickly identify the strain of mycobacteria and detect RIF resistance. This method has high sensitivity and specificity (Ioannidis et al. 2010; Helb et al. 2010). The test is available at an affordable price for high TB burden countries, and staff with minimal training can use the system. This method is recommended for use in county-level laboratories in developing countries.

17.8 The Application of New Technologies and Responses to Potential Challenges

Current methods of TB diagnosis include sputum smear, sputum culture, strain identification, and drug susceptibility testing. These diagnostic methods have been used for many years in TB laboratories where appropriate facilities and equipment are available. The current protocols for patient discovery, registration, reporting, transfer, treatment, and management are based on these diagnostic methods and are controlled by the corresponding rules and regulations. The adoption of new detection technologies will require an appropriate policy environment and a rational

regulatory framework. If new detection technology is to be introduced into the laboratory at all levels, we will need to identify the challenges that arise at each level during the evaluation process. Common challenges include a shortage of equipment and human resources, insufficient financial resources, and inadequate biosecurity and personal protection. In facing these challenges, the Chinese government has put great emphasis on the application and promotion of new technologies. It has invited experts to discuss the policy environment needed to promote the technology and provided support for the transformation of laboratories and the procurement of new technology and equipment.

17.9 Areas Requiring Further Research

17.9.1 Latent M. tuberculosis

The ability of *M. tuberculosis* to exist as a latent infection inside a patient's body is one of the reasons that a prolonged course of chemotherapy is necessary, which often results in poor treatment efficacy and high likelihood of relapse. Therefore, studies on *M. tuberculosis* latency may have important implications for both the prevention and treatment of TB, and a high priority should be placed on these studies.

17.9.2 Transcriptional and Posttranscriptional Factors

Studies on transcriptional and posttranscriptional factors in active and latent TB infections may help clarify the principles of TB latency. Looking for molecular markers of latency could provide a theoretical basis for TB prevention and diagnosis. Attention should also be given to studies on the transformation of *M. tuberculosis* from latent to active TB. Such studies could provide the basis for predicting which patients are likely to develop active TB and inform a subsequent treatment plan.

17.9.3 The Role of Chemically Modified Proteins

Studies of chemically modified proteins in *M. tuberculosis* have shown that phosphorylation, methylation, acetylation, and other modifications play an important role in the expression of proteins. Recent advances in proteomic methods could provide a map of protein modification under different conditions, which, combined with a study of the phenotypic characteristics of *M. tuberculosis*, may help us to

understand the mechanisms of transcriptional regulation. Metal ions play an important role in the growth and metabolism of *M. tuberculosis*. Magnesium ions are essential for growth, and thus clarifying their role may open up a potential approach for developing new drugs (Demartino and Gillette 2007).

17.9.4 M. tuberculosis *Gene Functions*

More than 4000 genes have been identified through the sequencing of the *M. tuberculosis* genome but we only know the functions and roles of a small portion of these. The function of many genes and the interactions between them are not clear. As of yet a strong, effective, antigen-specific, host immune protective antigen has not found. The identification of such an antigen would benefit the development of new vaccines and diagnostic technologies with increased sensitivity and specificity. The development of new drugs, which often rely on an in-depth understanding of genetic structure and function, would also benefit from gene function studies.

17.9.5 Pathogenic Mechanisms

Currently, many aspects of the interaction between TB hosts and pathogenic mechanisms are not clear. Many questions remain to be answered. We still don't fully understand the mechanisms that cause differences in the protective immune responses to TB. What is the mechanism and nature of latent tuberculosis infection, and why do only a small percentage of latent TB cases become active? Why do clinical symptoms differ among TB patients? Why does the efficacy of the BCG vaccine vary between populations?

17.9.6 The Role of Lipid Metabolism in TB Infection

Analysis of lipid metabolism may have a significant impact on the development of diagnostics and treatment for *M. tuberculosis* infection. Lipids play an important role in growth, response to stress, and drug resistance (Darwin et al. 2003). Lipids that are secreted can function as signaling molecules, which play a role in the process of infection. Therefore, analysis of fatty acid and lipid metabolism in a variety of environments, such as latent infections, active infections, and patients undergoing drug therapy, may be important. Of particular interest are the changes in lipids that are specific to mycobacteria and that may play a role in the biology of the host–pathogen relationship. This could also provide guidance in identifying new targets for anti-TB drug development.

17.9.7 Mycobacterium *Growth*

The slow growth of *M. tuberculosis* greatly complicates bacteriological testing by extending the time required for detection and drug sensitivity testing. On the other hand, many nontuberculous mycobacteria are fast-growing, and while the two types of mycobacteria are highly similar at the genomic level, the propagation rates are drastically different. Therefore studies on differences in transcription may reveal the basis for the differences in replication rate, which are closely related to the immune status of infected individuals (Gill et al. 2009).

17.9.8 Other

New research on TB immunity and pathogenesis should be directed towards further clarifying gene functions related to the protective host immune response and to the mechanisms related to *M. tuberculosis* latency.

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Chapter 18
TB Clinical Trials Conducted in China: The History and Future of the Beijing Tuberculosis and Thoracic Tumor Research Institute

Lizhen Zhu and Mengqiu Gao

18.1 An Overview of Clinical Trials Investigating Anti-TB Drugs

Before the establishment of China's State Food and Drug Administration (SFDA), medical research in China was conducted by national tuberculosis (TB) hospitals or hospitals with drug research or drug development units. These controlled clinical trials did not go through a formal government approval process and lacked inspection and supervision during their implementation. When isoniazid was first manufactured in China for treatment of TB in 1953, the Ministry of Health approved research projects in 32 hospitals. The purpose of these studies was to determine the function and the appropriate dosages of isoniazid when used as an anti-TB drug in Chinese patients. These clinical trials, which included 451 TB patients, determined the dosage range of isoniazid to be 2–6 mg/kg/day. In 1955, two groups (one led by Delong Zhang and the other by Song Li) verified the role of isoniazid in TB control in China (Guo and Zhang 1955; Li et al. 1955). Additional research validated the advantages of combination therapy in treating TB and proved that combination therapy can prevent drug resistance (Li et al. 1955; Tam et al. 1997). Based on these studies, a standard chemotherapy treatment was developed in which streptomycin, isoniazid, and salicylic acid were used in combination for 12–18 months or in some cases for 24 months. After 1977, a wide range of medical research and formal clinical trials were conducted on a variety of domestic and imported drugs, such as rifapentine (RFT) and rifampicin (R).

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China's Ministry of Health established the new national regulatory agency, the State Food and Drug Administration (SFDA), in 1983 to be responsible for approving new drugs and vaccines. In 1986, the Ministry of Health designated the Beijing Tuberculosis and Thoracic Tumor Research Institute (now the Beijing Chest Hospital) and the First Hospital of Chongqing Medical University as Clinical Pharmacology Centers for the study of TB. Since then, clinical trials involving TB drug development must obtain SFDA pre-approval and must be conducted in Clinical Pharmacology Centers in accordance with SFDA guidelines. Over a dozen TB chemotherapy clinical trials have been completed since the SFDA was established (see Table 18.1).

Two diagnostic products have been tested in clinical trials and clinically validated under SFDA supervision: the *Mycobacterium Tuberculosis* Nucleic Acid Amplification (PCR) Fluorescence Detection Kit and the *Mycobacterium Tuberculosis* TB-SA Antibody Clinical Diagnostic Kit, both manufactured by Sichuan Chengdu Yongan Pharmaceutical Co., Ltd and approved by SFDA in 2006. Two international, multicenter clinical trials, each investigating a different drug for the treatment of drug-resistant TB (OPC-67683 and TMC-207), were started in 2008 and are ongoing. Sponsored by Otsuka Pharmaceutical and Janssen Research and Development, these trials include sites at the Beijing Chest Hospital, Shanghai Pulmonary Hospital, Nanjing Chest Hospital, Shandong Chest Hospital, and Fuzhou Pulmonary Hospital.

18.2 Clinical Trial Design

Under the SFDA, new drug applications include two parts: an investigational new drug (IND) submission and a new drug application (NDA). In order to ensure the quality of new drugs, the IND must be in compliance with good laboratory practice (GLP), and the NDA must be conducted according to good clinical practice (GCP). Therefore, before TB-related clinical trials can be conducted, applicants must show positive results in biological studies and animal experiments, as well as acceptable results from studies of the drug's pharmacodynamics, pharmacologics, pharmacokinetics, and toxicology. If the results of such developmental research are positive, the applicant can report the preclinical research data to the SFDA in a clinical trial application for the new drug.

After SFDA approval, phase I, phase II, and phase III clinical trials can be conducted. While each phase has a different focus and purpose, the most important goal of all phases is to verify the safety and efficacy of the drug. Phase I clinical trials are designed to determine a safe dosage range and identify potential side effects. Phase II clinical trials are designed to confirm safety and efficacy. Phase III clinical trials are designed to monitor side effects and compare the drug to other treatment regimens in an expanded number of cases. All clinical trials conducted on new drugs must be managed by one of China's Clinical Pharmacology Centers and carried out in at least three independent clinical sites.

Table 18.1 A summary of National Collaborative Group clinical trials

	Trial	Sponsor/PI	Publication (s)
1978–1987	The first clinical trial of short-course chemotherapy of pulmonary TB	National Tuberculosis Short-course Chemotherapy Collaborative Group (PI: Yan Biya)	A study on short-course chemotherapy in pulmonary TB patients (Yan and Zeng 1982)
			The first batch of short-course chemotherapy of TB research report 5-year follow-up (Yan et al. 1993)
1982–1986	The second clinical trial of short-course chemotherapy of pulmonary TB	National Tuberculosis Short-course Chemotherapy Collaborative Group (PI: Yan Biya)	Preliminary results on second batch pulmonary TB patients with short-course chemotherapy (National Tuberculosis Short-course Chemotherapy Collaborative Group 1984)
1983–1988	The third clinical trial of short-course chemotherapy of pulmonary TB	National Tuberculosis Short-course chemotherapy Collaborative Group (PI: Yan Biya)	The curative effect observation rifandin in the treatment of 332 cases of pulmonary TB (National Cooperative Group on Clinical study of Rifadin 1982)
1983–1988	The fourth clinical trial of short-course chemotherapy of pulmonary TB	National Tuberculosis Short-course Chemotherapy Collaborative Group (PI: Yan Biya)	Results not published
1984–1997	The fifth clinical trial of short-course chemotherapy of pulmonary TB	National Rifapentine Collaborative Group (PI: Yan Biya)	A controlled clinical study on domestic rifapentine capsule in the treatment of TB (National Rifapentine Collaborative Group 1992)
			Controlled clinical trial of rifapentine given once weekly or fortnightly in 6-month regimens for the treatment of bacillary TB (Zhu and Yan 1997)
			A series study of domestic rifapentine in the treatment of TB (National Rifapentine Collaborative Group 1997)
1996–1998	To verify the antituberculous activity of fixed-dose compounds rifater/rifinah	Zhu Lizhen	Controlled clinical study on efficacy of fixed-dose compounds rifater/rifinah in antituberculous chemotherapy (Zhu et al. 1998)
			Controlled clinical study on efficacy of fixed-dose compounds rifater/rifinah in antituberculous chemotherapy—results at 2 years (Zhu et al. 2000)

(continued)

Table 18.1 (continued)

	Trial	Sponsor/PI	Publication (s)
2006–2008	A clinical trial on domestic four-drug fixed-dose combination in pulmonary TB	Zhu Lizhen	Feasibility study of domestic four-drug fixed-dose combination under DOTS as initial treatment in patients with smear positive pulmonary TB (Ma et al. 2010).
2002–2003	A random, open, parallel multicenter case–control study on injection of rifampicin in the treatment of pulmonary TB	Zhu Lizhen	A short-time clinical study on the efficacy of homemade sterilized powder for injection of rifampicin in the treatment of pulmonary TB (Gao et al. 2006a)
2002–2005	A clinical trial of rifabutin (RFB) in the treatment of multidrug-resistant TB	Zhu Lizhen	A controlled clinical trial of long-course chemotherapy regimens containing rifabutin in the treatment of multidrug resistant pulmonary TB (Zhu et al. 2006)
2005–2006	A multicenter randomized, double-blind, parallel group trial to evaluate the safety, efficacy of rifapentine hydrochloride capsule in patients with pulmonary TB	Zhu Lizhen	Results not published
2001–2002	A multicenter single-blind randomized, open, clinical trial to evaluate the efficacy of traditional Chinese medicine Qi Jia Yi Li Fei capsule in adjuvant treatment of pulmonary TB	Zhu Lizhen	Results not published
2001–2002	A multicenter, single-blind, randomized, open, parallel-controlled clinical trial to evaluate the efficacy of traditional Chinese medicine Fei tai capsule in adjuvant treatment of pulmonary TB	Zhu Lizhen	Observation in short-term efficacy and safety of adjuvant treatment in pulmonary TB with traditional Chinese medicine Fei tai capsules (Gao et al. 2006b)
2000–2001	Clinical verification study of human interleukin-2 in the adjuvant treatment of pulmonary TB	Zhu Lizhen	A controlled clinical study on the efficacy of recombinant human interleukin-2 in the treatment of pulmonary TB (Chu et al. 2003).
1996–1998	A clinical trial of *Mycobacterium vaccae* in the treatment of pulmonary TB	Luo Yongai	Immunotherapeutic effect of *Mycobacterium vaccae* on primary pulmonary TB. (National Cooperative Group on Clinical Study of *Mycobacterium Vaccae* Vaccine 2001)

PI principle investigator

18.2.1 The Roles and Responsibilities of Clinical Pharmacology Centers

The designated Clinical Pharmacology Center works in collaboration with research and development agencies and is responsible for designing the experimental protocol as well as generating informed consent forms (ICF), case report forms (CRF), and random number tables. The center is also responsible for the clinical trial organization, technical guidance, summary and evaluation of experiments, and making a conclusive report to the SFDA. All the clinical trials should be conducted with the approval of an Independent Ethics Committee (IEC).

Each clinical trial is a collaboration between a Clinical Pharmacology Center and three or more multicenter clinical pharmacology sites. During the experimental process, each site must be monitored by an internal drug research and development unit, which is validated by the SFDA. Each unit that participates in the clinical trial is responsible for implementing the experimental plan, obtaining signed ICFs, and then observing, recording, and reporting on the administration of treatment as well as the occurrence of any adverse events (AE). The Clinical Pharmacology Center must also satisfy SFDA mandatory inspections and fill out observation forms, which must retain the original documentation and data.

18.2.2 Clinical Trial Protocol

Clinical trials must be implemented with blind trial technique and randomized parallel groups. As with all types of clinical trials, the number of subjects should be sufficient to generate statistically significant results. An experimental plan must contain the inclusion criteria, exclusion criteria, withdrawal criteria, drug supply and dose, treatment scheme, outcome measures, assessment of response, criteria for adverse reactions, and statistical measures designed by statistics experts.

The clinical trial protocol should include the following items: name of sponsoring agency, names of cooperating agencies, background, purpose, clinical trial design (including the total number of samples, the number of research centers, timeline, and random groups), choice of subjects, inclusion criteria, exclusion criteria, withdrawal criteria, experimental protocol (including the name, dose, and usage of drug), observation items, management design, efficacy evaluation (standards and content), management plan for monitoring subject compliance, drug adverse reaction surveillance, research procedure, data management plan, statistical analysis, quality control and quality assurance plan, organization and responsibilities within the trial, timeline for the trail, the role of each agency involved in the trial, and the signature of the supervisor of each agency involved in the trial.

In compliance with the current international standard practices and the national regulatory requirements, an informed consent document is required. This is given to all subjects and states the purpose of the trial, the treatment process, the benefits and

possible risks, the compensation and the voluntary nature of the trial, and the opportunity to withdraw at any time.

18.3 Anti-TB Drug Research

The earliest randomized controlled clinical trials in China began in 1948, though they were basically conducted as ordinary medical research. In the early 1960s, a medical research study compared the effect of isoniazid alone in the treatment of TB with the effects of streptomycin (S), isoniazid (H), and sodium para-aminosalicylate (PAS) in combination. The study demonstrated that combination therapy not only had better efficacy but also helped prevent drug resistance. As a result, a combination treatment of S/H/PAS over the course of 12–18 months became the standard chemotherapy treatment for TB in China. In many cases, PAS was replaced with thiosemicarbazone (TB1) as a function of patient tolerance. This chemotherapy regimen was used routinely through the 1960s and most of the 1970s, achieving an efficacy of between 95 % and 98 % (Li and Xiao 1962). This treatment was highly effective in smear-positive patients, and with the extension of treatment, significantly reduced the relapse rate of TB after chemotherapy. Chemotherapy was effectively the cure for TB at that time. A report from the Beijing Red Star Commune Hospital in 1973 stated that 79.4–88.8 % of TB patients receiving isoniazid and TB1 treatment in a setting other than a hospital became TB sputum negative, indicating that this could be the main treatment for TB in rural areas where the local economy was depressed and medical facilities were limited.

In the 1960s, Professor Anyu Ming of the Beijing Tuberculosis and Thoracic Tumor Research Institute took the lead in exploring the dose requirements of adding streptomycin injections to the combination therapy for treating TB. He tested a daily dose of 0.75 g of streptomycin given by intramuscular injection compared to the standard dose of 1 g. He found that the lower intramuscular dosing mitigated eighth cranial nerve toxicity while achieving the same efficacy as the standard 1 g oral dose. Professor Ming did not formally publish the data; however, Zenglu Ma verified this result and reported it at the Hangzhou Tuberculosis Conference (Ma and Qin 1979) where the new dosage was approved. To this day, this is the standard protocol when streptomycin is added to TB chemotherapy.

18.3.1 Clinical Trials in the 1970s and 1980s

The National Collaborative Group on Clinical Tuberculosis Studies was founded in 1978. Led by the Beijing Tuberculosis Research Institute (now Beijing Chest Hospital), with more than 20 participants from provinces and cities across China, the National Collaborative Group conducted a series of clinical studies on TB chemotherapy (see Table 18.1). The primary goals were to test short-course

chemotherapy regimens for new and existing drugs, assess various doses and dosing schedules, and expand the number and category of test subjects to further evaluate safety and efficacy. These studies lasted 20 years and were conducted in a sequential manner. All the studies used the prospective, randomized, controlled research method and involved treatment with different courses, different drug combinations, and different drug intervals. The elements of these studies were evaluated in initial treatment cases and retreatment cases.

Each study investigated a different aspect of treatment, and even though each was part of a larger overall study, they were all conducted independently in order to reach their own independent conclusions. Each project had a thorough plan, method, and procedure for implementation.

18.3.1.1 Clinical Study of the Anti-Tuberculosis Function of Rifampicin

The National Collaborative Group of Investigations on Short-Course Chemotherapy conducted a study over 9 consecutive years from 1978 to 1987. The study was designed to assess the feasibility of short-course chemotherapy regimens containing rifampicin (R). One of the initial studies compared the efficacy and feasibility of two different short-course rifampicin regimens. A total of 554 patients were divided into a 6-month test program group, a 9-month test program group, and a standardized chemotherapy reference group. The treatment groups received either 6HRE (see Table 18.2) or 9HRE, and the reference group was given the standard chemotherapy of the time, 3HSP/15HP. The conversion rates to negative sputum were 97.0 % for the 6-month group, 98.2 % for the 9-month group, and 92.0 % for the 18-month reference group. This indicated that the 6-month and 9-month short-course chemotherapy programs containing rifampicin were just as effective as the 18-month standard chemotherapy program. It also showed that short-course chemotherapy was feasible in China in the absence of pyrazinamide (PZA), which was not available in China at that time (Yan and Zeng 1982).

After finishing the course of therapy, subjects were followed up for 5 consecutive years. The 5-year relapse rates for 481 of the cases were 5.8 % for the 6-month test regimen, 1.1 % for the 9-month test regimen, and 3.9 % for the 18-month reference group. Yan et al. concluded that the 9-month program containing rifampicin was efficacious and that the long-term follow-up could be reduced to 3 years (Yan et al. 1993).

18.3.1.2 Clinical Study of Changes in the Administration of Rifampicin

Conducted from 1982 to 1986, the aim of this study was to compare different routes of administration, different delivery methods, and the relationship between the course of treatment and the effectiveness of initial treatment and retreatment of pulmonary TB. At the time of this study, there was very little data on retreatment of relapsed or reinfected TB patients after prior short-course chemotherapy. China's first epidemiological survey of TB retreatment patients indicated that the

Table 18.2 Drug abbreviations used in clinical treatment regimens

Drug abbreviations	
Amikacin	AMK, AK
Ethambutol	E, EMB
Isoniazid	H, INH
Sodium aminosalicylate	PAS, P
Levofloxacin	V, LFX
Prothionamide	PTO, TH
Pyrazinamide	Z, PZA
Rifabutin	RFB
Rifadin	D
Rifampicin	R
Rifapentine	L
Streptomycin	S
Isoniazid aminosalicylate tablets	Pa

Drug regimens are written in the text using single letter abbreviations for each drug. The numeral prefix denotes the number of months of treatment in the regimen. Drugs are taken daily unless otherwise specified. Intermittent therapy is indicated by a subscript, which notes the number of times a drug is administered per week

smear-positive rate was 45.6 %. The chemotherapy programs were 2SHRZ/4SHR, 2EHRZ/4EHR, 2SHRZ/6$S_3H_3R_3$, or 2EHRZ/6$E_3H_3R_3$. Initial treatment and retreatment cases used the same chemotherapy programs. Of the 1187 cases, the conversion rates to smear negative sputum were 96.3–99.5 % (728 total cases) in the initial treatment groups and 93.2–95.7 % (301 total cases) in the retreatment groups. The conclusion was that orally administered ethambutol is an alternative to streptomycin for short-course chemotherapy and that long-course chemotherapy treatment with ethambutol is feasible with intermittent therapy starting after the 2 month intensive phase of treatment.

18.3.1.3 Clinical Study of the Function of a New Anti-TB Drug, Rifadin

Rifadin was a new kind of rifampicin drug available in 1976 and developed by Antibiotics Industry Research Institute in Sichuan Province, China. The minimum inhibitory concentration (MIC) was less than that of rifampicin (R). An observational study of short-course chemotherapy treatment of TB with rifadin (D)-containing tablets (isobutyl piperazine rifamycin) was conducted from 1983 to 1988. The study was designed to compare the efficacy of rifadin-containing regimens to those containing rifampicin. The initial treatment groups were given 2SHDZ/4HD, 2SHDZ/4HDE, or 2SHRZ/4HRE. The retreatment groups were given 2SHDZE/7$H_3D_3E_3$, 2SHDZE/5HDE, or 2SHRZE/5HRE. Of the 447 cases in initial treatment, the conversion rate to negative sputum for groups containing rifadin was 92.8–92.9 %, and the conversion rate for the control group containing

rifampicin was 92.2 %. Of the 111 cases in retreatment, the sputum conversion rate of the test group containing rifadin was 74.2–90.2 %, and sputum conversion rate for the control group containing rifampicin was 76.9 % (National Cooperative Group on Clinical study of Rifandin 1982). As a part of this work, a separate drug metabolism study compared rifampicin tablets and capsules. During therapeutic drug monitoring, 4-h plasma concentration determinations were made. The results showed that treatment with rifampicin capsules resulted in plasma concentrations of 12.8 μg/ml, and treatment with rifampicin tablets resulted in plasma concentrations of 4.0 μg/ml. It was determined that the poor treatment outcomes in this group were a result of using rifampicin tablets (National Cooperative Group on Clinical Study of Rifandin, unpublished data).

18.3.1.4 Clinical Study of Shortened and Intermittent Course Treatments and Expanding Indications for Rifampicin

This study investigated the efficacy of intermittent dosing, examined the application of short-course chemotherapy for heavy drinkers and individuals with diabetes mellitus and also explored the possibility of further expanding the indications for rifampicin treatment to tuberculous pleuritis, tuberculous meningitis, and tuberculous lymphadenitis. The initial treatment groups for pulmonary TB were $2S_3H_3R_3Z_3E_3/4S_3H_3R_3E_3$, 2SHRZE/3RHE, $2SHRZ/5HEDL_2$, and $2SHRZ/5H_2E_2R$. The initial treatment groups for tuberculous pleuritis were $1SHRZ/4RHE$ and $1SHRZ/4R_3H_3E_3$. The initial treatment groups for tuberculous meningitis were 2SHRZE/7HRE and 3SHRZE/6HRE. The initial treatment groups for lymph node TB were 2SHRE/4HR and $2SHRZ/4H_2DL_2$. The results from the 449 cases were as follows. The conversion rate to negative sputum in the initial treatment groups for pulmonary TB was 95.8–99.2 %. The recurrence rate of 418 cases at the 2-year follow-up was 3.13–3.19 %. The conclusion was that the whole intermittent program can be used for the treatment of pulmonary TB. The numbers of extrapulmonary TB cases, along with the alcoholic and diabetic cases, were too few to make any conclusions about treatment (Yan et al., unpublished data).

18.3.1.5 Clinical Studies of the New Anti-TB Drug, Rifapentine

In 1977, the Industrial Research Institute of Antibiotics in Sichuan, China, developed cyclopentyl-piperazine-rifamycin (rifapentine, L) for the treatment of TB. After preliminary clinical trials in 1984, three different treatment programs containing rifapentine were studied in large-scale clinical trials, using rifampicin as the standard for comparison.

In the first rifapentine study, 443 case subjects received a 9-month treatment of rifapentine as part of a standard drug regimen. After 1 month of treatment, patients either continued with rifampicin or took rifapentine intermittently. The regimens of the groups were $1LHZE/8L_1H_2E_2$, $1LHZE/8L_2H_2E_2$, $1RHZE/8L_2H_2E_2$, or 1RHZE/8RHE. The conversion rates to negative sputum were 99.3 % in the first regimen

group and 100 % in the remaining groups. These treatment programs were shown to have excellent efficacy after 3 years; the regimen groups had bacteriological relapse rates of 0.8 %, 2.3 %, 0 %, and 1.4 %, respectively. This demonstrated that rifapentine was a long-lasting, highly effective anti-TB drug (National Rifapentine Collaborative Group 1997).

The second rifapentine study, which included 554 total cases, assessed the efficacy and feasibility of a shortened course of rifapentine treatment. The experimental treatment programs were $2SHRZ/5L_2H_2E_2$ and $2SHRZ/4L_2H_2$. The corresponding reference programs were $2SHRZ/5R_2H_2E_2$ and $2SHRZ/4R_2H_2$. The conversion rates of patients to *M. tuberculosis* negative sputum were 96.4 and 98.5 % in the test groups and 95.8 and 98.3 % in the respective reference groups. The 3-year bacteriological relapse rates were 3.7 and 4.2 % in the experimental groups and 1.0 and 1.6 % in the reference groups (National Rifapentine Collaborative Group 1997).

The third rifapentine study was designed to assess an increase in the rifapentine treatment interval and a reduction in the number of drugs. The test treatment programs were $1LHZE/8L_1H_2E_2$, $2SHRZ/4L_1H_2$, and $1SHRZ/4L_{1/2}H_2$. The reference programs were 1RHZE/8RHE and $2SHRZ/4R_2H_2$. The negative sputum conversion rates in the test groups ranged from 98.5 to 100.0 % (302 total cases), and in the rifampicin-containing control groups the conversion rates were 100.0 % (114 total cases). The 3-year bacteriological relapse rate among all groups ranged from 1.6 to 4.8 %. These results indicated that rifapentine is safe, reliable and has the advantage of requiring lower and less frequent doses (National Rifapentine Collaborative Group 1997). Further studies confirmed the high efficacy and long-lasting effect of rifapentine (Zhong 1995; Weng 1992).

Dr. Shiu-lun Chan[1] in Hong Kong reported that rifapentine produced by a Chinese pharmaceutical company had lower bioavailability than the imported drug and that an increased dosage was necessary to get the same bacteriological conversion rates. Dr. Chan and C.M. Tam confirmed this in a study (Tam et al. 1997). Four lots of Chinese produced rifapentine were administered to 287 TB patients at the same dose level. The reference cohort received rifapentine from the Merrell Dow Research Institute (Winnersh, UK). The content of rifapentine in participant's serum samples was measured during the course of the study. The bioavailability of the Chinese rifapentine was around 66–74 % compared to the imported rifapentine. To equal the therapeutic level of 600 mg of imported rifapentine, the dose of the Chinese rifapentine had to be increased to 750 mg (Tam et al. 1997).

A follow-up pharmacokinetic study at the Beijing Tuberculosis and Thoracic Tumor Research Institute and the Liaoning Academy of Traditional Chinese Medicine Laboratory of Clinical Pharmacology did not find a significant difference between rifapentine from a different manufacturer (Industrial Research Institute of Antibiotics, Sichuan, China) and imported rifapentine (Tang et al. 2009). The measured peak time (Tmax), half-life (t1/2), peak concentration (Cmax), concentration–time area under the curve (AUC), and relative bioavailability were not significantly different. The data from this study approximated pharmacokinetic data reported

[1] Due to variations in Pinyin conversion, Dr. Shiu-lun Chan is also written as Dr. Zhaolin Chen.

elsewhere (Langdon et al. 2004). There were no other comparative studies examining the bioavailability of rifapentine produced in China; however, subsequent studies on the effectiveness of rifapentine produced in China produced good results (Liu and Chen 1996).

18.3.2 More Recent TB Chemotherapeutic Clinical Trials Conducted in China

In the 1980s, many countries began using fixed dose drug combinations (FDCs) to treat TB. Compared to a HRZE regimen that may include taking medicine three times and about a dozen tablets daily, patients taking FDCs may take a total of 4–5 pills once a day. Patients taking FDCs have lower default rates. The FDC tablet Rifinah® contains a complex of rifampicin and isoniazid. The FDC tablet Rifater® contains a complex of rifampicin, isoniazid, and pyrazinamide. In 1996, Hoechst Marion Roussel Inc. sponsored a study in which 308 cases of sputum positive pulmonary TB were randomly assigned to two groups: the FDC group (2Rifater/4Rifinah) or the reference group (2HRZ/4HR). The conversion rates to *M. tuberculosis* negative sputum were 98.7 and 97.5 %, respectively (Zhu et al. 1998, 2000).

18.3.2.1 Domestic FDC Complex

In 2006, 225 newly diagnosed cases of TB were treated with a domestic FDC composed of four drugs recommended by the WHO for the treatment of TB: isoniazid, rifampicin, pyrazinamide, and ethambutol. The FDCs were formulated at two specified doses: isoniazid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg, and ethambutol 275 mg for the intensive phase of treatment and isoniazid 100 mg with rifampicin 150 mg for the continuation phase. The FDC treatment regimen was 2HRZE(FDC)/4HR(FDC), and the reference regimen (using individual doses for each drug) was 2HRZE/4HR. In this study, the test group and reference group achieved conversion rates to *M. tuberculosis* negative sputum of 99.1 % and 96.5 %, respectively (Ma et al. 2010). This validated the anti-TB efficacy of this domestic FDC regimen.

18.3.2.2 Injectable Rifampicin

From 2002 to 2003, the Beijing Chest Hospital conducted clinical trials on the efficacy and safety of domestic injectable rifampicin (stored as a freeze-dried powder) for the treatment of TB. Newly diagnosed sputum positive pulmonary TB patients (n = 121) were randomly divided into test (61) and reference (60) groups. The test group was treated with domestic rifampicin, and the reference group was treated

with imported rifampicin. All other treatment parameters were the same. Adverse reactions, X-ray results, and conversion rates to *M. tuberculosis* negative sputum were monitored over the course of treatment. The conversion rates to *M. tuberculosis* negative sputum of the test and reference groups were 86.21 and 91.38 %, respectively ($\chi^2 = 0.780$, $p = 0.377$). The conversion rates to negative *M. tuberculosis* sputum culture were 91.38 % and 93.10 %, respectively ($\chi^2 = 0.120$, $p = 0.729$). The significant efficiency by X-ray examination was 82.76 % and 70.69 %, respectively ($\chi^2 = 2.365$, $p = 0.124$). The incidence of adverse events was 8.20 % in the test group and 11.67 % in the reference group. The study concluded that for the treatment of TB, there were no significant differences between the efficacy, safety, and tolerance of the domestic and foreign preparations of rifampicin (Gao et al. 2006a).

18.3.2.3 Rifabutin Versus Rifapentine

The clinical trial conducted in 2006 included the treatment of 130 MDR-TB patients with rifabutin. Patients in the experiment group were treated with isoniazid (H), aminosalicylate tablets (PA), levofloxacin (LFX), ethambutol (E), prothionamide (TH), amikacin (AMK), and rifabutin (RFB) for 18 months. In the reference group, RFB was replaced with rifapentine. The resulting sputum conversion rates of 75.0 % in the experimental group and 65.08 % in the reference group suggested that rifabutin is an effective replacement for rifapentine in the treatment of MDR-TB (Zhu et al. 2006).

18.3.2.4 Rifapentine Hydrochloride Capsules

In 2004, a clinical trial tested the use of rifapentine hydrochloride, which is a more stable formulation than rifapentine. The regimen for both groups was the same ($2HL_2ZE/4HL_2$); however, one group received rifapentine hydrochloride capsules and the other group received rifapentine. The conversion rate to *M. tuberculosis* negative sputum for both groups was 100 %, indicating that the efficacy of rifapentine and rifapentine hydrochloride capsules is same (Zhu et al., unpublished data).

18.3.2.5 The Adjuvant Effect of *Qi jia bu yin li fei* Capsules in TB Therapy

The clinical trial, conducted from December 2001 to November 2002, randomly placed newly diagnosed patients and retreatment patients into two groups; one with an experimental adjuvant from Traditional Chinese Medicine ($n = 101$) and one without it ($n = 105$). Newly diagnosed patients in the test group were given $2HL_2Z$ + *Qi jia bu yin li fei*/$4HL_2$ + *Qi jia bu yin li fei.* Patients in the reference group were given $2HL_2Z$ + placebo/$4HL_2$ + placebo. Retreatment patients in the test group were given $3HL_2ZV$ + *Qi jia bu yin li fei*/$4HL_2V$ + *Qi jia bu yin li fei*, and those in the reference group were given $3HL_2ZV$ + placebo/$4HL_2V$ + placebo.

The conversion rates to negative sputum culture in the newly diagnosed test and placebo groups were 90.91 % and 89.66 %, respectively. The conversion rates to negative sputum culture in the retreated test and placebo groups were 82.75 % and 75.00 %, respectively. This result suggests that traditional Chinese medicine may improve outcomes when used in combination with standard chemotherapy (Zhu et al., unpublished data).

18.3.2.6 The Adjuvant Effect of *Fei tai* Capsules

In May 2001, five hospitals conducted a multicenter, random, parallel-controlled clinical trial of the adjuvant effect of *Fei tai* capsule on TB chemotherapy. The treatment regimens for the newly diagnosed patients were: $2HL_2Z$ + *Fei tai*/$4HL_2$ + *Fei tai* (test group) and $2HL_2Z$ + placebo/$4HL_2$ + placebo (reference group). Retreatment patients in the test group were given $3HL_2Z(TH)V$ + *Fei tai*/$5HL_2V$ + *Fei tai* and those in the reference group were given $3HL_2Z(TH)V$ + placebo/$5HL_2V$ + placebo. The conversion rates to negative sputum culture in the newly diagnosed test and reference groups were 100.0 % and 96.2 %, respectively. The conversion rates to negative sputum culture in the retreatment test and reference groups were 90.0 % and 85.0 %, respectively. Although *Fei tai* capsules did not significantly improve efficacy in this study, there was evidence for increased foci absorption and an improvement in symptoms related to TB drug toxicity. There were no adverse reactions in patients taking *Fei tai* capsules for extended periods of time (Gao et al. 2006b).

18.3.2.7 The Adjuvant Effect of Recombinant Human Interleukin-2 (IL-2) on TB Therapy

In 2001, the Beijing Tuberculosis and Thoracic Tumor Research Institute administered a clinical trial carried out at five clinical centers. TB patients (n = 209) were divided into a test group (106) and a reference group (103). The test regimen was $3PaZ(TH)L_2VE(AK)/4PaL_2V$, plus patients received 200,000U IL-2 daily for the first month, stopped IL-2 for the second month, and then continued IL-2 through the end of the treatment. The reference group received chemotherapy only: $3PaZ(TH)L_2VE(AK)/4PaL_2V$. When the treatment program was finished there were 203 evaluable patients: 103 in the treated group and 100 in reference group. The conversion rates to negative sputum culture after 1 month of treatment were 33.3 % in the test group and 7.2 % in the reference group. After 2 months of treatment, the conversion rates to negative sputum culture were 69.4 % in the test group and 44.9 % in the reference group. The difference was significant ($p < 0.01$). Upon completion of treatment, the efficacies as determined by X-ray were 64.1 % in the test group and 36.0 % in the reference group ($p < 0.001$). There was a significant increase in CD4, CD4/CD8, and NK cells in the test group as compared to the reference group after being treated for 3 and 7 months ($p < 0.01$). The soluble IL-2 receptor (sIL-2R) of the test group decreased after 3 months of therapy and the difference was significant

($p < 0.05$). There were no serious adverse events, and the study concluded that recombinant human IL-2 could augment the treatment of TB as a safe, reliable biological agent (Chu et al. 2003).

18.3.2.8 *Mycobacterium vaccae* as a Treatment for TB

In the late 1990s, an anti-TB treatment of injectable *M. vaccae* was developed by the Long Coma Biopharmaceutical Company (China). The Chinese National Institutes for Food and Drug Control and the 309th Hospital of Chinese People's Liberation Army completed a wide range of basic research on the manufacturing process of this product. The active ingredients were purified, and the route of administration was improved to greatly increase the efficacy and reduce side effects. A national multicenter clinical study was conducted by the Pulmonary Hospital of Chongqing Medical University. The study, which included 568 TB cases, showed that in combination with standard chemotherapy treatment, this product (designated MVaccae) can significantly enhance the cellular immune function in patients with pulmonary TB. It was also shown to shorten the initial treatment of TB; speedup sputum conversion, cavity closure, and lesion absorption; and improve drug treatment, rehabilitation, and cure rate of multidrug resistant pulmonary TB (National Cooperation Group on Clinical Study of *Mycobacterium vaccae* Vaccine 2001). MVaccae passed an SFDA review in 1998, and a license was granted to the Long Coma Biopharmaceutical Company for the use of this drug in clinical applications.

18.4 Clinical Trials of Diagnostic Reagents

In December 2002, the SFDA issued the "In vitro Diagnostic Reagents Registration Regulation (Draft)." According to the regulation, the clinical trial must be done in the cases of the registration for new diagnostic reagents, or a diagnostic ragents which have had national standards, or any change in raw material, response mode or threshold for an on sale diagnostic reagents.

According to information released by the SFDA in 2004, clinical studies were scheduled for a mycobacterium antibody diagnostic kit (ELISA) and a *M. tuberculosis* nucleic acid amplification (PCR) fluorescent detection kit. In April 2007, the State Food and Drug Administration issued the publications "In vitro Diagnostic Reagents Registration for Trial Implementation," "Clinical Study of In vitro Diagnostic Reagents Technical Guidelines," and "In vitro Diagnostic Reagents Written Instructions Guiding Principle." These documents were produced to enhance management of the registration of in vitro diagnostic reagents and clarify the specific requirements for clinical research. In 2010, an ELISPOT-based TB detection kit (T-SPOT®.TB) manufactured by Oxford Immunotec, Inc. was allowed to register according to the clinical validation regulations in China.

18.5 Closing

In 1978, clinical testing of the new anti-TB drug rifampicin began in China. Based on the results of those clinical trials, China implemented a nationwide TB treatment program that incorporated HRZE combined treatment. Since then, early sputum conversion rates at the end of the initial phase of treatment of pulmonary TB have normally been above 90 % and approached 97 % after the full course of treatment. At the same time, recurrence rates have averaged less than 5 %. Short-course FDC chemotherapy using rifampin and rifapentine was subsequently adopted in some cities and provinces. In the early 1990s, China's Ministry of Health implemented a nationwide TB Program to promote the use of new drug therapies and new technologies through the implementation of standardized clinical trials. This has played a significant role in controlling the spread of TB in China. Currently, both foreign and domestic drugs and diagnostic reagents must go through China's SFDA approval process, which is carried out at one of the national TB clinical pharmacology centers. The number of TB clinical pharmacology centers has doubled since 1986. With the implementation of higher standards and close monitoring of the clinical trial process, China hopes to improve the credibility, efficacy, and safety of new drugs and diagnostics.

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Chapter 19
Adapting DOTS for Application in Rural China

Guiying Wu and Xinping Zhao

19.1 The DOTS Program

In 1993, the World Health Organization (WHO) declared a worldwide state of emergency for tuberculosis (TB). In the next year, WHO promoted Directly Observed Therapy, Short Course (DOTS) management as a global TB control strategy (WHO 1993, 1994; Bayer and Wilkinson 1995). DOTS management is used in 182 nations around the world. The implementation of DOTS management has increased the progress of TB prevention and cure programs in many nations and has had a positive effect on TB control (Behera 2009; Raviglione and Pio 2002; Dye et al. 1998). There were, however, several challenges in the implementation of DOTS management. In undeveloped nations or regions, implementation of DOTS management increased the work burden on the medical staff and also made treatment inconvenient for patients living far away from hospitals (Barends 2002; Portero et al. 2002; Peterson et al. 1999). This reduced compliance, especially among patients with little education or with little knowledge of TB. Patient noncompliance has been shown to be the most important factor in TB therapy failure and the development of drug resistance (Lipsitch and Levin 1998). Effective patient therapy management is critical. Appropriate measures should be applied based on the specific requirements of each nation because of differences in political milieu, social/cultural issues, and ethical values (Walley 1997).

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19.1.1 Problems in DOTS Management in China

In 1991, the WHO applied DOTS management to China. By 1992, DOTS management had a positive effect on China TB control, to the credit of the World Bank TB Control Project (also referred to as the Bank V Project). The 2004 China TB Control Project Social Assessment Study showed that the following five problems hampered the quality of patient therapy management under DOTS (Ministry of Health Disease Control Division 2006):

1. Most TB patients in the study (70.0 %) declared that it was not necessary to take medicine with direct supervision.
2. The rate of TB patients receiving the entire supervision of the actual treatment was not high. Of the 877 TB patients in the survey, 55.8 % (489 patients) were self-medicated, 24.3 % (213 patients) were supervised by family, and 19.9 % (175 patients) were monitored by village doctors.
3. The interactive behaviors between the village doctors and the patients were constrained by the traditional views on TB. Of the 2418 residents in the survey, 57.1 % thought having TB would lead to discrimination by their neighbors.
4. TB patients had little knowledge of TB control. The project results showed that 52.3 % of patients did not know that TB was infectious and that 46.2 % of patients did not know that curing TB was the primary goal of the doctor.
5. The effect and potential of the doctors in the county TB control were not fully realized. The DOTS management required the county TB control doctor to guide the first identified TB patients in treatment, but did not require doctors to be responsible for patient therapy management and completion.

19.1.1.1 Adverse Factors Affecting Patient Compliance in TB Treatment

The course of the first anti-TB drug treatment for TB patients is 6 months. During the primary course, the outcome of the treatment is affected by many factors. These include doctor factors such as ethical behavior, diagnosis and treatment, health education, and drug delivery, as well as patient factors such as privacy issues, consistent time of dosing, and disease symptoms. All factors affect patient therapy management (Table 19.1).

19.1.2 The Importance of Exploring Effective TB Treatment Management

With the advent of anti-TB drugs and advances in chemotherapy, TB is no longer an incurable disease. However, in some areas, the rate of medication compliance among TB patients is only 51 %. Among TB patients in Chinese hospitals, 100 % were medication compliant, but compliance dropped to 38 % after discharge (Huang

Table 19.1 Factors affecting compliance in the initial diagnosis system supervision and management mode of TB therapy

Doctor's factors	Examples	Patient's factors	Examples
Ethical behavior	Responsibility, ethics, language guide	Privacy issues	Marriage, work, social connections
Diagnosis/treatment	Treatment level	Medicine	Working hours conflicting with the medication time
Medicine	Effect, price	Disease symptoms	Light symptoms leading to inattention; heavy symptoms leading to panic, anxiety
Response to adverse reaction	Approach, effect	Economic conditions	Costs of treating adverse reactions
Health education	Knowledge of prevention, teaching method	Comprehension of TB control knowledge	Low comprehension leading to poor compliance; high leading to good compliance

2006). Medication compliance is the most important aspect of TB control because it decreases the incidence of drug resistance. The medication management skills of county and village TB control doctors can vary due to regional, economic, cultural, and transportation factors. This leads to different treatment outcomes. It is a major social concern how to resolve the problems in TB patient treatment management and to explore and build an effective TB treatment management model.

19.2 The Pilot Program: Supervision and Management Skills of County TB Doctors for Promoting Compliance in TB Patients During the Initial Visit

The problem of how to resolve the shortcoming in implementation of the DOTS management model has been studied by various scholars (Wang et al. 2008; Wu et al. 2008). From 2008 to 2009, a research team combining members from the social medicine and health economics departments at the School of Public Health at Fudan University carried out a pilot program titled "Supervision and Management Skills of County TB Doctors for Promoting Compliance in TB Patients during the Initial Visit." The program was designed to address the five problems with DOTS implementation in China (see Sect. 19.1.1). The program's goal was to increase TB patients' therapy knowledge, awareness of behaviors that can transmit TB, and compliance with doctor supervision and regular treatment. The research ideas and design were as follows:

1. The county TB control doctors read a manual, written by the research team, outlining the "Principles and Methods for Doctors Guiding TB Outpatients in Self-Medication Management." The county TB control doctors were to learn the principles, requirements, and importance of first visit responsibility and understand the factors in TB patient psychology, behavior, social fields, and treatment compliance. The county TB control doctors were taught the relationship between attitude, language, and treatment level of doctors in the medical practice and TB patient treatment compliance. The county TB control doctors were also required to master the theory, procedures, and techniques of improving TB patient self-medication management.
2. The research team designed a picture album which included TB Patient Treatment Knowledge and Self-Management guidelines, in line with regulations and applicable principles and requirements of the TB patient national management (Ministry of Health Disease Control Division 2000) using vivid, easily understood illustrations designed to minimize cultural barriers. Theoretically, the picture album was the bridge between doctors and patients, helping patients grasp knowledge of medicine management, TB control, and healthy behavior. The album taught the importance of regular medicine therapy and communication with doctors to cure the patient. It was intended to encourage behaviors for self-medication and upgrade the knowledge and ability for self-medication management, with the aim of equipping patients to finish their treatment course.
3. The research team designed specific guidelines for the county TB control doctors in the pilot program. The doctors were to monitor the entire supervision of TB patient medication according to these guidelines.

19.2.1 The Manual for Doctors to Educate TB Outpatients on Self-Medication Management

This manual was prepared to educate doctors in county institutes of TB control on the methods and requirements for self-medication management and patient psychology. The manual is divided into three parts containing a total of 15 items (Table 19.2).

19.2.2 TB Patient Treatment Knowledge and Self-Management Picture Album

The TB Patient Treatment Knowledge and Self-management Picture Album is divided into five parts for a total of 18 items. The album uses one picture at a time to demonstrate the National Tuberculosis Treatment Regulations and Tuberculosis Medication Management Knowledge and Behavior Requirements for patients. The

Table 19.2 The contents of the manual for doctors to educate TB outpatients on self-medication management

Items	Content
Part I	
Theory behind doctor's guiding patients on self-medication management	1. Current status and problems in medication management of TB patients
	2. Function of city and county doctors for guiding patients on self-medication management
	3. Rules and regulations for doctors guiding patients on self-medication management
	4. Patient self-medication management behaviors and psychological factors
Part II	
The effect doctors have on patient behavior with respect to medication management	1. Cognitive interaction between doctors and patients
	2. Doctor's influence on patient's willpower
	3. Doctor's influence on the patient's fear of disease
	4. The effect of doctor's speech on the quality of patient's regular therapy
	5. The effect of the medical professional's level of treatment on patient compliance
	6. The effect of doctor's behavior on patient therapy
Part III	
The principle and requirement of doctors guiding patients on self-medication	1. Six elements of doctors guiding patients during onset of medication
	2. Six medication management problems doctors deal with upon patient's return visit
	3. The need for doctors to teach patients medication management by communicating information
	4. The need for doctors to record the patient's self-medication process
	5. The need for doctors to summarize and collect the experience of patients who finish treatment

album also has a recording section to help monitor the patient's medicine and any adverse reactions. The album standardizes the doctors' approach to informing patients, supplements the doctors' guidance, and increases the patient's understanding of the treatment. The album is not only a persuasive tool for the doctor to introduce TB control knowledge and guide the patient in self-medication, but it also facilitates the patient's understanding of the material and reinforces the patient's grasp of TB control with help from the medicine recording section. The album has become a bridge between patients and doctors by allowing doctors to monitor the patients' treatment from the monthly medicine recorder in the album (Table 19.3).

Table 19.3 Content of TB patient treatment knowledge and self-management picture album

Items	Content
Part I	
Diagnosis and treatment	1. TB control and cure institutions are TB diagnosis and treatment medical institutions
	2. Diagnostic criteria and requirements
	3. Treatment programs and requirements
Part II	
Knowledge of treatment management	1. Patient self-management and behavior requirements
	2. Sputum sampling during medication and requirements
	3. The essentials during patient medicine
	4. The consequences of irregular medication
	5. Common adverse reactions after medicine
	6. Adherence to medication leads to family happiness
	7. Adverse drug reactions requiring follow-up with the doctor
Part III	
Family supervision and care	1. Monitoring patients taking medications, care for patients nutrition, exercise, and mental health
	2. The effect of indoor ventilation on the domestic spread of TB
	3. Monitoring patient's adherence to treatment regimens for 6 months and to teach that to complete is to win
Part IV	
Consequences of irregular medication	1. Increases the probability of resistance to anti-TB drugs
	2. Increases the difficulty of curing the patient
Part V	
Policy of free services	1. Free drugs
	2. Free sputum test
	3. Free chest X-ray

19.2.3 Guidelines of the Initial Diagnosis System Supervision and Management Model

The county doctors should educate the TB patient during the first visit, direct the patient to study the album for 30 min, and then call the patients once a week during the 2-month boost period in order to increase compliance and monitor any adverse reactions. Upon the patient's return visit, doctors should ask the patient about medication conditions and review the album's content page by page in order to assess the patient's grasp of the methods of TB medicine treatment management. If the patient's responses are not complete, further guidance is necessary. The specific contents and methods of monitoring and management routes designed by the current study are shown in Table 19.4.

Table 19.4 Routes of "supervision and management skills of doctors promoting compliance in TB patients during the initial visit"

Therapy stages	Time	Guidance content
Stage 1		
First visit review of album	30 min	1. Guide patient on the rules of medication and methods for handling their side effects; explain how to keep the record of medication
		2. Explain the relationship between pathogenesis and medicine and issues of infectious TB
		3. Describe the specific time requirements of sputum testing as well as the specific time and location for taking anti-TB drugs
		4. Train family supervisors to supervise patient taking medications and take care of patient's nutrition and rest
		5. Ease TB patient's fear of having the disease and discuss adverse psychological effects of not paying attention to the disease
Stage 2		
Boost phase at 2 months telephone guidance	5 min per week	1. Ask patient about medication times and doses, whether medication records were kept, and whether clinical symptoms have improved
		2. Ask patient about adverse reactions; if any, specific guidance on handling adverse reactions is necessary
		3. Encourage patients to adhere to the complete treatment course
Stage 3		
Boost phase at 2 months return visit guidance	10 min per visit	1. Ask patient about medication rules and principles and understand condition of patient's medicine treatment and self-management
		2. Ask patient about adverse reactions; if any, specific guidance on handling adverse reactions is necessary
		3. Check medication records and understand the patient's psychological reflection on the medication
Stage 4		
Consolidation phase at 4 months return visit guidance	Once a month 10 min per time	1. Know whether the patient missed medication and whether clinical manifestations eased and disappeared
		2. Check if any adverse reactions improved after treatment and whether sputum was taken when the doctor indicated
		3. Check medication records, ask if patient has the idea to give up on the treatment
		4. Encourage patients to adhere to medication treatment to overcome TB

19.2.4 Educating Patients in TB Control and Healthy Behavior

Due to differences in culture, education level, and living conditions, patients can have different levels of understanding of medical issues. Of particular importance is a patient's awareness of his or her own habits and viewpoints that determine their own behavior. The pilot program was designed to improve the county TB control doctors' medical and health education skills. The Picture Album guides doctors in teaching patients about TB control. The album allows patients to improve their understanding of TB control and have a constant reference for information. This leads patients to finish their course of medicine. The current project utilizes the measures of good eating behavior and indoor ventilation, minimizing coughing, and instilling healthy sleeping habits and adherence to medication.

19.2.4.1 Promoting Regular Consumption of Medicine

TB patients are prone to irregular consumption of medicine due to internal and external factors, many of which stem from a lack of knowledge concerning TB control. Especially during the first 2 months of the consolidation phase, interrupting the regular intake of medicine results in TB's rapid reproduction and growth, promoting drug-resistant strains in the lungs and hampering the treatment. The pilot program requires that the patients receive regular supervision by county TB control doctors, record the times that medicine is taken, and enforce the importance of regular intake of medicine.

19.2.4.2 Enforcing Patient Compliance in Providing a Sputum Sample on Schedule

TB patients must provide a sputum sample on schedule during the medicine treatment so that the doctors know the disease status and can verify or improve the quality of treatment. The Ministry of Health regulates that the primary TB treated patients should provide a sputum sample at the end of the second, fifth, and sixth months of chemotherapy to check the effect of treatment. Each time point requires a night and a morning sputum sample. The pilot program teaches patients the importance of on schedule sputum testing and encourages compliance of providing the sputum samples on schedule.

19.3 Comparing the Pilot Program to DOTS

In comparing the program "Supervision and Management Skills of County TB doctors for Promoting Compliance in TB Patients during the Initial Visit" with the DOTS management model, we focused on the effect of supervision and

management on patient medication behavior. The pilot program required that the TB control doctors supervise patients for 6 months following the management course. The model also required doctors to follow a format of treatment and management and highlighted specific times for educating patients and assessing the level of patient mastery for TB control. The DOTS management model required county doctors to inform first-time TB patients about the treatment plan, but did not require the doctors to assess whether or not the patients memorized or fully understood the treatment plan.

In the most recent study, two counties in the provinces of Chongqing and Zhejiang were evaluated. In each province, one county served as the study group and the other as the control group (in Chongqing, county A is the study group and county B is the control; in Zhejiang province, county C is the study group and county D is the control). The control groups in each of the two counties in the same province were basically the same in terms of economic status, human resources, and work ability. The study groups followed the "Supervision and Management Skills of County TB doctors for Promoting Compliance in TB Patients during the Initial Visit" protocol, whereas the control groups followed the DOTS management protocol. A prospective cohort study was used, and the patients who finished a 6-month treatment course were surveyed.

19.3.1 Evaluation of the Pilot Program

The "initial visit" TB patients who had finished a 6-month treatment course for their diseases were clearly analyzed for several parameters according to the model of TB control and cure management that was carried out. Surveys were completed and most of the patients returned valid survey forms (892 total; 266 in county A, 310 in county B, 124 in county C, and 192 in county D). We know the relationship between each management model and the rate of patient compliance, rate of on time sputum testing, and the rate of finishing the course of medicine.

19.3.1.1 Eating Behavior

In Chongqing county A (study group), 88.35 % of the patients ate separately from their families after diagnosis, as compared to 59.68 % of patients in the B county (control group). The rate of separate eating in the study group was higher than the rate in the control group, and the difference was statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 64.60$, $P < 0.001$). In Zhejiang province, 83.07 % of patients in the C county ate separately from their families after diagnosis, as compared to 69.27 % of patients in the D county (control group). The rate of separate eating in the study group was higher than the rate in the control group, and the difference was statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 9.72$, $P < 0.001$). Eating behavior survey results are listed in Table 19.5.

Table 19.5 Separate eating after diagnosis with TB

Patient eating separately?	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
	# (%)	# (%)	# (%)	# (%)
Yes	235 (88.35)	185 (59.68)	103 (83.07)	133 (69.27)
No	28 (10.53)	124 (40.00)	19 (15.32)	58 (30.21)
No data	3 (1.12)	1 (0.32)	2 (1.61)	1 (0.52)
Total	266 (100.00)	310 (100.00)	124 (100.00)	192 (100.00)

Table 19.6 Maintenance of indoor ventilation after diagnosis with TB

Families maintaining indoor ventilation	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
	# (%)	# (%)	# (%)	# (%)
Yes	264 (99.25)	284 (91.61)	122 (98.38)	189 (98.44)
No	0 (0.00)	25 (8.07)	1 (0.81)	3 (1.56)
No data	2 (0.75)	1 (0.32)	1 (0.81)	0 (0.00)
Total	266 (100.00)	310 (100.00)	124 (100.00)	192 (100.00)

19.3.1.2 Ventilation

In the A county (study group) of Chongqing, 99.25 % of families maintained indoor ventilation after patient diagnosis, as compared to 91.61 % of families in the B county (control group). The rate of maintaining indoor ventilation in the study group was higher than the rate in the control group, and the difference was statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 20.12$, $P < 0.001$). In Zhejiang province, 98.38 % of families in the C county maintained indoor ventilation when the diseases of the subjects in the families were identified, as compared to 98.44 % of families in the D county (control group). The difference was not statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 1.89$, $P > 0.05$). Almost all of the families in the study group maintained indoor ventilation, and the rates were only slightly higher in the study group (see Table 19.6).

19.3.1.3 Coughing

In the A county (study group) in Chongqing, 98.50 % of patients did not cough near or speak loudly to others after diagnosis, as compared to 73.23 % of patients in the B county (control group). The rate of low cough behavior or speaking loudly in the study group was higher than the rate in the control group, and the difference was statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 74.77$, $P < 0.001$). In Zhejiang province, 90.32 % of patients in the C county did not cough or speak loudly to others after diagnosis, as compared to 82.29 % of patients in the D county

Table 19.7 Coughing or speaking loudly after diagnosis with TB

Patients not coughing or speaking loudly to others	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
	# (%)	# (%)	# (%)	# (%)
Yes	262 (98.50)	227 (73.23)	112 (90.32)	158 (82.29)
No	2 (0.75)	81 (26.13)	12 (9.68)	34 (17.71)
No data	2 (0.75)	2 (0.64)	0 (0.00)	0 (0.00)
Total	266 (100.00)	310 (100.00)	124 (100.00)	192 (100.00)

Table 19.8 Sleeping behavior after diagnosis with TB

Patients sleeping apart	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
	# (%)	# (%)	# (%)	# (%)
Yes	217 (81.58)	207 (66.77)	106 (85.48)	167 (86.98)
No	45 (16.92)	101 (32.58)	9 (7.26)	24 (12.50)
No data	4 (1.50)	2 (0.65)	9 (7.26)	1 (0.52)
Total	266 (100.00)	310 (100.00)	124 (100.00)	192 (100.00)

(control group). The rate of low cough behavior or speaking loudly in the study group was higher than the rate in the control group, and the difference was statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 3.91$, $P = 0.04$, see Table 19.7).

19.3.1.4 Sleeping Behavior

In the study group of Chongqing, 81.58 % of patients slept apart from family members after diagnosis, as compared to 66.77 % of patients in the B county (control group). The rate of healthy sleeping behavior in the study group was higher than the rate in the control group, and the difference was statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 19.13$, $P < 0.01$). In Zhejiang province, 85.48 % of patients in the C county slept apart from family members after diagnosis, as compared to 86.98 % of patients in the D country (control group). The difference was statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 12.81$, $P < 0.01$; see Table 19.8).

19.3.1.5 Identification of the Key Factor in Medicine Management

In the A county (study group) in Chongqing, 96.61 % of patients thought that the key factor in recovery from infection was adhering to medication, as compared to 85.48 % patients in the B county (control group). The rate in the study group was higher than the rate in the control group, and the difference was statistically significant by exact probabilities test ($P < 0.01$). In Zhejiang province, 94.36 % of patients

Table 19.9 Patient survey responses to identifying the key factor in medicine management

Key factor of recovery	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
	# (%)	# (%)	# (%)	# (%)
More rest	1 (0.38)	13 (4.20)	0 (0.00)	17 (8.85)
More nutrition	4 (1.50)	19 (6.13)	0 (0.00)	26 (13.54)
Reduce work hours	0 (0.00)	4 (1.29)	0 (0.00)	4 (2.09)
Adherence to medication	257 (96.61)	265 (85.48)	117 (94.36)	144 (75.00)
Physical exercise	3 (1.13)	5 (1.61)	0 (0.00)	1 (0.52)
No data	1 (0.38)	4 (1.29)	7 (5.64)	0 (0.00)
Total	266 (100.00)	310 (100.00)	124 (100.00)	192 (100.00)

in the C county thought the key factor in recovery was adhering to medication, as compared to 75.00 % patients in the D county (control group). The rate of knowing the key factor in recovery in the study group was higher than the rate in the control group, and the difference was statistically significant by exact probabilities test ($P < 0.01$, see Table 19.9).

19.3.1.6 Patient Dosing Compliance

In the A county (study group) of Chongqing, 90.23 % patients took medicine regularly and followed the doctors' guidance, as compared to 69.35 % patients in B county (control group). The difference was statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 37.94$, $P < 0.001$). In Zhejiang province, 85.48 % of patients in the C county took medicine regularly and followed the doctor's guidance as compared to 75.52 % patients in the D county (control group). The difference was statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 33.02$, $P < 0.001$; see Table 19.10). The main reason given for irregular consumption of medicine was patients forgetting a dose. Patients in the study group took medication regularly at a significantly higher rate than in the control groups. The DOTS (control) groups' guidelines ask village doctors to supervise patients taking medicine during the 2-month consolidation phase, but in the actual treatment, the rate of village doctor supervision was not high.

19.3.1.7 Providing Sputum Sample on Schedule

In the A county (study group) of Chongqing, 95.49 % of patients provided a sputum sample on schedule, as compared to 64.52 % patients in the B county (control group). The difference was statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 92.59$, $P < 0.001$). In Zhejiang province, 89.52 % of patients in C county provided

Table 19.10 Regular consumption of medicine

Patient takes medicine as prescribed	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
	# (%)	# (%)	# (%)	# (%)
Yes	240 (90.23)	215 (69.35)	106 (85.48)	145 (75.52)
No	24 (9.02)	91 (29.36)	5 (4.03)	45 (23.44)
No data	2 (0.75)	4 (1.29)	13 (10.49)	2 (1.04)
Total	266 (100.00)	310 (100.00)	124 (100.00)	192 (100.00)

Table 19.11 Providing a sputum sample on schedule

Patients providing a sputum sample on schedule	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
	# (%)	# (%)	# (%)	# (%)
Yes	254 (95.49)	200 (64.52)	111 (89.52)	162 (84.38)
No	8 (3.01)	109 (35.16)	9 (7.26)	29 (15.10)
No data	4 (1.50)	1 (0.32)	4 (3.22)	1 (0.52)
Total	266 (100.00)	310 (100.00)	124 (100.00)	192 (100.00)

a sputum sample on schedule, as compared to 84.38 % patients in D county (control group). The difference was statistically significant by Pearson χ^2 test ($p < 0.05$; $\chi^2 = 7.57$, $P < 0.05$). The main reasons for not providing a sputum sample on schedule were inconvenience due to traffic, lack of notification from the doctor, and patient's determination that the sample was not necessary (Table 19.11).

19.3.1.8 Completing Medicine Treatment

In the A county (study group) of Chongqing, 100.00 % of 266 patients completed the medicine treatment, compared to 94.52 % of 293 patients in the B county (control group). The difference was not statistically significant by Fisher's exact probabilities test ($p > 0.05$; $P = 0.08$). In Zhejiang province, 100 % of 124 patients in the C county completed the medicine treatment, compared to 94.79 % of 182 patients in the D county (control group). The difference was not statistically significant by Fisher's exact probabilities test ($p > 0.05$; $P = 0.28$). The rates of completing the medicine treatment in both study groups and control groups were high; all above 95 % and in the study groups, the rates were 100 % (see Table 19.12). Patients in both the study and control groups completed treatment at higher rates than in previous surveys (see Sect. 19.1.1).

Table 19.12 Completion of medicine treatment

Patients completing chemotherapy	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
	# (%)	# (%)	# (%)	# (%)
Yes	266 (100.00)	293 (94.52)	124 (100.00)	182 (94.79)
No	0 (0.00)	17 (5.48)	0 (0.00)	10 (5.21)
Total	266 (100.00)	310 (100.00)	124 (100.00)	192 (100.00)

19.3.2 Cost Evaluation of the Pilot Program

It is very important to analyze a study from different perspectives. As for calculation of cost, there are different results when analyzed from different perspectives. The cost of the current study is calculated from the perspectives of three different entities: the medical institution (the TB hospital and other health providers), the patient, and society (Fang 1999; Gong et al. 2003).

19.3.2.1 Calculation of Cost from the Institute's Perspective

Because the diagnosis and treatment of TB is relatively standard, the cost of the TB treatment service is divided into categories such as outpatient services, chest X-rays, sputum examination, drugs, village health visits, Picture Album, etc. The cost of a single item is calculated first; then, the accumulated cost is calculated based on the typical treatment plan for the initial treatment of a TB patient.

Through the institute cost questionnaire, six categories of costs were considered: labor, administration, operations, materials, consumables, and the maintenance and depreciation of fixed assets in the country TB control institute. Housing depreciation was calculated over a 40-year period with a depreciation rate of 2.5 %. The depreciation of equipment and permanent assets was calculated over a 12.5-year period with a depreciation rate of 8.0 % (see Tables 19.13, 19.14, 19.15, and 19.16). As to the departments providing services indirectly (such as Finance, General Services, Personnel), the cost was divided based on the number of staff into outpatient department, X-ray department, and biochemical lab, which provide direct services. The cost of item services is the result of the cost of the business sections divided by the number of times of service provided by the department items per year.

The cost calculated from the institute's perspective of curing a primary treated TB patient is 844.91 RMB in the A county (study group), of Chongqing, as compared to 922.34 RMB in the B county (control group), an increase of 77.43 RMB over the study group. In Zhejiang province, the cost to cure a primary treated TB patient is 745.63 RMB in the C county, as compared to 886.24 in the D county (control group), an increase of 140.61 RMB over the study group. The county TB control doctors in the study group were asked to guide the first visiting patients for 30 min using the Picture Album and talked with the return visit patients for 10 min.

Table 19.13 Six categories of cost in the outpatient department of county TB control institute

	Chongqing		Zhejiang	
Cost (RMB)	A county (study group)	B county (control)	C county (study group)	D county (control)
Labor	17,5056.00	256,370.00	27,119.17	347,833.00
Office	0.00	30,589.20	84,331.59	118,260.00
Operations	19,527.78	22,114.29	164,385.00	178,424.00
Materials	0.00	10,842.86	26,400.00	19,672.00
Consumables	200.00	441.94	26,800.00	43,280.00
Maintenance and depreciation	24,130.00	43,827.38	130,531.92	53,447.04
Total	218,913.78	364,185.67	459,567.67	760,916.04

Table 19.14 Six categories of cost in the X-ray room of county TB control institute

	Chongqing		Zhejiang	
Cost (RMB)	A county (study group)	B county (control)	C county (study group)	D county (control)
Labor	75,648.00	69,480.00	3013.24	65,768.00
Office	0.00	15,294.60	0.00	24,232.00
Operations	11,716.67	11,057.14	7371.43	34,185.00
Materials	12,000.00	5421.43	30,800.00	48,240.00
Consumables	100.00	220.97	0.00	2600.00
Maintenance and depreciation	23,600.00	49,089.46	70,904.72	33,903.40
Total	123,064.67	150,563.60	112,089.39	208,928.40

Table 19.15 Six categories of cost in the biochemical lab of county TB control institute

	Chongqing		Zhejiang	
Cost (RMB)	A county (study group)	B county (control)	C county (study group)	D county (control)
Labor	71,736.00	68,342.00	3013.24	58,969.00
Office	0.00	15,294.60	0.00	24,112.00
Operations	11,716.67	11,057.14	7371.43	34,373.00
Materials	144200.00	5421.43	0.00	30,460.00
Consumables	200.00	220.97	0.00	3200.00
Maintenance and depreciation	27,150.00	52,947.01	370,945.83	29,978.32
Total	255,002.67	153,283.15	381,330.50	181,092.32

Compared with the control groups, the study groups pay more attention to the instructions of the county TB control doctors. The time taken to guide patients and the cost of outpatient care is more than in the control groups. In the study group, the county and village doctors did not visit the patients in their homes, and the cost of this item is zero, but the Album was delivered to the first visiting patient's homes

Table 19.16 Six categories of cost in the nonbusiness section of county TB control institute

	Chongqing		Zhejiang	
Cost (RMB)	A county (study group)	B county (control)	C county (study group)	D county (control)
Labor	183,816.00	548,004.00	89,083.74	817,164.00
Office	18,000.00	107,062.20	355,901.00	339,589.00
Operations	27,138.90	77,399.98	55,3461.08	431,205.00
Materials	0.00	36,423.68	133,000.00	16,912.00
Consumables	500.00	1546.80	0.00	31,670.00
Maintenance and depreciation	22,550.00	36,558.39	177,273.17	119,397.16
Total	252,004.90	806,995.08	1,308,718.99	1,755,937.16

Table 19.17 The cost to cure a TB patient with a primary infection: the institute's perspective

	Chongqing		Zhejiang	
Cost (RMB)	A county (study group)	B county (control)	C county (study group)	D county (control)
Outpatient services	18.01	15.69	19.25	17.82
Chest X-ray	22.79	27.17	23.10	25.89
Sputum test	9.72	6.55	6.84	8.29
Drugs	512.00	543.00	434.00	487.20
Country (village) health visits	0.00	80.00	0.00	80.00
Album	5.00	0.00	5.00	0.00
Other	46.00	49.00	41.00	42.00
Total	844.91	922.34	745.63	886.24

Note: Total cost includes 7 outpatient visits, 3 chest X-rays, and 9 sputum tests. "Other" costs include infrastructure factors such as equipment maintenance and depreciation

and the cost was 5 RMB. In the control group, the patients were required to take medicine under the doctor's direct supervision and the village doctors visited the patient's families once a month and the cost was 80 RMB each time (Table 19.17).

19.3.2.2 Cost Calculation from the Patient's Perspective

To calculate the cost of curing TB from a patient's perspective, patients were given a treatment management questionnaire. Patients provided data on the amount they paid for treatment and associated expenses, medical costs, nutrition fee, and lost work from relatives who accompanied the patient. The formula for the patient perspective cost is:

The cost to cure a primary treated TB patient (patient perspective) = treatment costs (lab examination fee + drug fee + prevention and treatment costs of adverse reactions) + associated costs (traffic fee + accommodation costs) + loss of working costs + nutrition fee.

Table 19.18 The cost to cure a primary treated TB patient from the society perspective in the two models (in RMB)

	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
Patient perspective	1497.06	1728.78	1345.05	1595.28
Treatment costs	756.87	935.67	737.99	807.14
Institute perspective[a]	844.91	922.34	745.63	886.24
Society perspective	1585.10	1715.45	1352.69	1674.38

[a]See Table 19.17

Note that the treatment costs included in these calculations are covered by the government.

19.3.2.3 Cost Calculation from a Society's Perspective

From the society's perspective, the cost to cure a primary treated TB patient in different models was calculated. The society perspective combines the institute perspective and patient perspective. Because there are treatment costs incorporated into both the institute and patient perspective calculations, these costs need to be subtracted out to avoid duplication. The formula for the society perspective cost is:

The cost to cure a primary treated TB patient (society perspective) = the cost in patient perspective − treatment costs + the institute perspective

From a society's perspective, the cost to cure a primary treated TB patient is 1585.10 RMB in the A county (study group), of Chongqing, as compared to 1715.45 RMB in the B county (control group), an increase of 130.35 RMB over the study group. In Zhejiang province, the cost to cure a primary treated TB patient is 1352.69 RMB in the C county, as compared to 1674.38 RMB in the D county (control group), an increase of 321.69 RMB over the study group (see Table 19.18).

19.3.2.4 Analysis of the Results of the Costs of Two Models

The cost of complete treatment (cure) for the initial treatment of one TB patient from any given perspective is calculated as follows:

The cost of complete treatment for a primary treated TB patient = the average cost to cure a primary treated TB patient ÷ the percentage of patients completing treatment

The costs of curing a primary treated TB patient using the two medicine management models and calculated from the perspectives of the institute, patient, and society, respectively, were 844.91 RMB, 1497.06 RMB, and 1585.10 RMB in A county (study group) of Chongqing, compared to 969.56 RMB, 1817.28 RMB, and 1803.27 RMB in B county (control group). In Zhejiang province, the cost to cure a primary treated TB patient from the respective perspectives was 745.63 RMB, 1345.05

Table 19.19 The cost of complete treatment per primary treated TB patient in the two medicine management models (in RMB)

	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
Institute perspective	844.91	969.56	745.63	900.83
Patient perspective	1497.06	1817.28	1345.05	1621.55
Society perspective	1585.10	1803.27	1352.69	1701.95

RMB, and 1352.69 RMB in the C county, and 900.83 RMB, 1621.55 RMB, and 1701.95 RMB in the D county (control group, see Table 19.19). Regardless of the calculation from any perspective, the cost of curing a primary treated TB patient in the control groups is higher than in the study groups.

TB DOTS management requires that the patients take medicine under the direct supervision of the village doctor during the 2-month consolidation phase. But in the actual treatment, taking medicine under direct supervision of the village doctor is hard to apply. The current study shows that the rates of finishing treatment are high both in the study groups and in the control groups. But the cost of curing a primary treated TB patient in the study groups is obviously lower than in the control groups regardless of the institute, patient, or society perspective. All show that applying the "Supervision and Management Skills of County TB doctors for Promoting Compliance in TB Patients during the Initial Visit" is a more cost-effective approach.

19.3.2.5 Cost–Benefit Analysis

The results of the cost–benefit analysis reflect the currency unit. The benefit calculation generally includes three parts: direct benefit, indirect benefit, and intangible benefit. By the ratio of cost against benefit, we can compare not only different TB treatment management methods using currency unit conversion but also compare the investment and result of the TB treatment management method itself.

In the current study, the direct benefit of the pilot program was calculated using the DOTS management group as a baseline. Indirect benefit means the value generated by restored labor and general methods including human capital approach and estimates based on per capita GDP and per capita income, respectively. The subjects were mostly farmers, and therefore it was more reasonable to take rural per capita net income to estimate the indirect benefit. The intangible benefit is difficult to estimate meaningfully, and therefore such a benefit was not calculated.

19.3.2.6 Direct Benefit

The direct benefit was determined by defining the DOTS management reference as zero and calculating the difference between the costs of the DOTS and pilot programs. From the perspectives of the institute, patient, and society, the benefit of

Table 19.20 The direct benefit of complete treatment per primary treated TB patient using the two medicine management models (in RMB)

	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
Institute perspective	77.43	0.00	140.61	0.00
Patient perspective	231.72	0.00	250.23	0.00
Society perspective	130.35	0.00	321.68	0.00

curing a primary treated TB patient was 77.43 RMB, 231.72 RMB, and 130.35 RMB, respectively, in the A county (study group) in Chongqing. In Zhejiang province, the benefit of curing a primary treated TB patient was 140.61 RMB, 250.23 RMB, and 321.68 RMB, respectively, in the C county (see Table 19.20).

19.3.2.7 Indirect Benefit

Indirect benefit is estimated based on rural per capita net income as follows:

Loss of income (due to illness) = rural per capita net income × the rate of labor in TB patients × reduction in the loss of Disability Adjusted of Life Years (DALY)

In the A county (study group) of Chongqing, the rural per capita net income is 3335 RMB and the loss by curing a primary treated TB patient is 25,203.43 RMB, whereas in the B county (control group) the rural per capita net income is 3210 RMB and the loss due to curing a primary treated TB patient is 22,018.15 RMB. The loss in the study group was obviously more than in the control group. In Zhejiang province, the rural per capita net income is 9097 RMB and the loss by curing a primary treated TB patient is 70,871.32 RMB in the C county, while the rural per capita net income in the D county (control group) is 8921 RMB and the loss by curing a primary treated TB patient is 59,827.11 RMB. The loss in the study group was obviously more than in the control group (see Table 19.21).

19.3.2.8 Total Benefit

The total benefit is a combination of direct and indirect benefits:

The total benefit of complete treatment per primary treated TB patient = direct benefit + indirect benefit

The total benefit was calculated from institute, patient, and society perspectives. The total benefits calculated from different perspectives are nominally different in the study groups. In the A county (study group) of Chongqing, the total benefit was more than 25,000 RMB, as compared to 22,000 RMB for the B county (control group). In Zhejiang province, the total benefit was more than 71,000 RMB in the C county, while more than 59,000 RMB in the D county (control group). The total benefit in the study group was higher than in the control group (see Table 19.22).

Table 19.21 Indirect benefit of complete treatment per primary treated TB patient using the two medicine management models

	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
Rural annual net income per capita (RMB)	3335	3210	9097	8921
Proportion of TB patients in the labor force (%)	0.74	0.70	0.75	0.72
Loss of DALY (year)	10.21	9.80	10.39	9.31
Loss of income (RMB)	25,203.43	22,018.15	70,871.32	59,827.11

Note: The labor force is considered to be males 16–59-year-old and females 16–55-year-old. The rural annual net income per capita is based on 2008 figures

Table 19.22 Total benefit of complete treatment per primary treated TB patient using the two medicine management models (in RMB)

	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
Institute perspective	25,280.86	22,018.15	71,011.92	59,827.11
Patient perspective	25,435.15	22,018.15	71,121.55	59,827.11
Society perspective	25,333.78	22,018.15	71,193.00	59,827.11

Note that the control counties had slightly lower incomes and smaller proportions of TB patients in the workforce, and these factors, while small, affect the total benefit and are independent of the difference in TB treatment.

19.3.2.9 Cost–Benefit Analysis

We compared the two treatment management models by calculating the cost–benefit ratio of complete treatment per primary treated TB patient. The benefit of complete treatment per primary treated TB patient (total benefit divided by completed treatment cases) from the institute, patient, and society perspectives is 29.92 RMB, 16.99 RMB, and 15.98 RMB, respectively, per 1 RMB investment in the A county (study group) of Chongqing and 23.87 RMB, 12.74 RMB, and 12.84 RMB, respectively, per 1 RMB investment in the B county. In Zhejiang province, the benefit of curing a primary treated TB patient is 95.24 RMB, 52.88 RMB, and 52.63 RMB per 1 RMB investment in the C county, respectively, while 67.51 RMB, 37.50 RMB, and 35.73 RMB in the D county, respectively (see Table 19.23). The benefits per 1 RMB investment in the study groups were more than in the control groups, and it

Table 19.23 Total cost–benefit ratio of complete treatment per primary treated TB patient in the two medicine management models

	Chongqing		Zhejiang	
	A county (study group)	B county (control)	C county (study group)	D county (control)
Institute perspective	29.92	23.87	95.24	67.51
Patient perspective	16.99	12.74	52.88	37.50
Society perspective	15.98	12.84	52.63	35.73

showed that the model of the study groups was more effective in terms of cost–benefit ratio.

In the current study, the benefits per 1 RMB investment in the study groups were greater than in the control groups, regardless of the institute, patient, or society perspectives. It showed that the model of the study groups was more effective in cost–benefit ratio. The program, "Supervision and Management Skills of County TB doctors for Promoting Compliance in TB Patients during the Initial Visit" resulted in a smaller investment and gave more benefit than the DOTS TB treatment management model. The benefit was dozens of times as much as the investment.

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Part III

Chapter 20
BCG Immunization: Efficacy, Limitations, and Future Needs

Kwok Chiu Chang and Chi Chiu Leung

Abbreviations

BCG	Bacille Calmette–Guérin
BMRC	British Medical Research Council
CI	Confidence interval
HCW	Healthcare workers
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IUATLD	International Union against Tuberculosis and Lung Disease
NRAMP	Natural resistance-associated macrophage protein
TB	Tuberculosis
UNICEF	United Nations Children's Fund
USPHS	United States Public Health Service
WHO	World Health Organization

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20.1 Historical Background

Bacille Calmette–Guérin (BCG), a live attenuated vaccine, is one of the oldest vaccines in the world. The original BCG strain was lost during World War I (1914–1918) (Lagrange 1984). Derived from a virulent strain of *Mycobacterium bovis* through 230 subcultures over 13 years by French investigators Calmette and Guérin (Sakula 1983), the first dose of BCG was orally given to a human volunteer in 1921 (Calmette 1931a; Weill-Hallé and Turpin 1925). The safety of BCG was severely challenged when contaminated BCG killed 72 children in Germany from 1929 to 1930 (Calmette 1931b; Lange; 1930; Moegling; 1935).

With early evidence for efficacy among student nurses in Norway (Heimbeck 1936), BCG was increasingly used in Europe. The demonstration of high efficacy of BCG against tuberculosis (TB) in trials initiated by the British Medical Research Council (BMRC) in the 1950s led to routine BCG vaccination in the majority of the world (WHO 1972; Hart and Sutherland 1977). Since BCG was incorporated into the Expanded Program on Immunization's (EPI) infant vaccination schedule in 1974, use of BCG has globally expanded.

Owing to the lack of protection shown in BCG trials conducted by the United States Public Health Service (USPHS) in the early 1950s (Comstock and Palmer 1966), the USA has adopted a policy of selective BCG vaccination among high-risk populations and based their TB control strategy partly on rapid diagnosis and early treatment of TB disease and partly on preventive treatment of infected individuals (CDC 1996). The Netherlands has followed suit.

20.2 Global Use of BCG

As the only licensed vaccine against TB, BCG is one of the most widely used vaccines in the world. In the 1990s, approximately 100 million children received BCG vaccine every year (WHO 1997). Based on WHO/UNICEF estimates, global coverage of BCG vaccination during infancy further increased from 81 % in 1990 to 88 % in 2009 (WHO 2010b). More than 120 million doses are now used every year (Ritz et al. 2008).

BCG vaccination policies vary across different countries by the BCG strain (Ritz and Curtis 2009) as well as the vaccination schedule (Brewer et al. 1995). Four BCG strains account for more than 90 % of the vaccines currently in use: Pasteur-1173 P2, Copenhagen-1331, Glaxo-1077, and Tokyo-172. The Pasteur strain is currently the international reference strain of vaccine (Milstien and Gibson 1990). BCG vaccination schedules can be classified into four main groups (Fine et al. 1999): vaccination once only at birth, vaccination once only in childhood or adolescence, multiple doses involving boosters, and selective vaccination among high-risk groups. Vaccination once only at birth is the schedule currently recommended by the WHO EPI) and practiced in most countries. A study by Ritz and Curtis found that

44 % of countries reportedly used more than one BCG strain within a 5-year period (Ritz and Curtis 2009). To help clinical interpretation of diagnostic tests as well as the design and evaluation of new TB vaccines, Zwerling and coworkers have created the first searchable online database of global BCG vaccination policies and practices which also captures any applicable changes (Zwerling et al. 2011).

BCG vaccination policies have changed with TB incidence. To improve cost-effectiveness, nine countries have shifted from universal to selective BCG vaccination in response to declining TB incidence rates: Spain in 1981; Denmark in 1986; Austria in 1990; Germany in 1998; and Isle of Man, Slovenia, UK, Finland, and France between 2005 and 2007 (Zwerling et al. 2011). According to the International Union against Tuberculosis and Lung Disease (IUATLD), universal BCG vaccination may be stopped when an efficient notification system is in place with one of the following conditions: (1) the average annual notification rate of smear-positive pulmonary TB is less than 5 per 100,000, (2) the average annual notification rate of tuberculous meningitis in children under 5 years of age is less than 1 per 10 million population over the previous 5 years, or (3) the average annual risk of tuberculous infection is less than 0.1 % (IUATLD 1994).

Over 30 countries have stopped BCG revaccination as increasing evidence demonstrated lack of additional protection (Zwerling et al. 2011).

BCG vaccination policies have also changed as a result of HIV infection. Being live attenuated, BCG can cause invasive and disseminated BCG disease among the immunocompromised, especially HIV-infected subjects. Before 2007, WHO recommended routine vaccination in TB-endemic countries in the absence of symptoms of HIV infection (WHO 2004). Since 2007, in response to evidence of an unacceptably higher risk of disseminated BCG disease among HIV-infected vaccinees (WHO 2007a), WHO has recommended that BCG vaccination of HIV-infected children be discontinued in TB-endemic countries (WHO 2007b). The IUATLD has suggested that neonatal BCG vaccination in TB-endemic areas be continued until programs are in place for selective deferral of BCG vaccination in infants exposed to HIV (Hesseling et al. 2008).

20.3 Efficacy of BCG

Most of the variations regarding global use of BCG across different countries may have stemmed from the partial and variable efficacy of BCG.

20.3.1 Initial Experience and Historical Cohort Trials

With preliminary evidence for the utility of BCG in protecting against TB among student nurses in the 1930s (Heimbeck 1936) and American Indians in the 1940s (Aronson 1948a, b), BMRC and USPHS set up major trials in the early 1950s to

further evaluate the efficacy of BCG against TB. Instead of drawing conclusive evidence for the protective efficacy of BCG, BMRC and USPHS demonstrated completely opposing findings. The use of Copenhagen strain against tuberculin-negative adolescents in BMRC trials efficaciously protected against TB, whereas the Park or Tice strains given to tuberculin-negative subjects by the USPHS demonstrated little protection. Two hypotheses were put forward to explain the discrepancy. One attributed the differences to variation between BCG strains (Hart 1967). The other considered environmental factors, especially environmental mycobacteria (Palmer and Long 1966). To evaluate these hypotheses, a large trial involving all age groups started in 1968 to compare two well-established BCG strains ("Paris/Pasteur" vs. "Danish/Copenhagen") in the Chingleput area of South India, where there is a high prevalence of environmental mycobacteria. A companion trial in an area in northern India with little environmental mycobacterial exposure was conceived but unfortunately aborted due to political unrest. The Chingleput trial revealed no evidence for the efficacy of either vaccine against pulmonary TB (Baily 1980; ICMR/WHO Scientific Group 1980). This set the scene for a series of clinical trials (WHO 1972; Bettag et al. 1964; Comstock et al. 1974, 1976; Comstock and Webster 1969; Frimodt-Moller et al. 1973; Rosenthal et al. 1961; Stein and Aronson 1953; Tripathy 1987; Vandiviere et al. 1973) and observational studies (Blin et al. 1986; Camargos et al. 1988; Canetti et al. 1972; Jin et al. 1989; Miceli et al. 1988; Murtagh 1980; Orege et al. 1993; Padungchan et al. 1986; Pönnighaus et al. 1992; Rodrigues et al. 1991; Shapiro et al. 1985; Tidjani et al. 1986; Wunsch Filho et al. 1990) that evaluated the efficacy of BCG in different populations of the world.

20.3.2 Efficacy and Impact of BCG Vaccination

Most studies were conducted among participants initially vaccinated during infancy and young childhood rather than adulthood. Vaccine efficacy rates are generally greatest within the few years following vaccination and most consistent against serious forms of TB in infants and young children (CDC 1996; Rieder 2008). Data are too few for evaluating the protective efficacy of BCG against other forms of extrapulmonary TB. On the other hand, the protective efficacy of BCG vaccination against pulmonary TB is highly heterogeneous with efficacy estimates ranging from below 0 % to approximately 80 % across clinical trials and observational studies (WHO 1972; Bettag et al. 1964; Blin et al. 1986; Comstock et al. 1974, 1976; Comstock and Webster 1969; Frimodt-Moller et al. 1973; Miceli et al. 1988; Orege et al. 1993; Putrali et al. 1983; Pönnighaus et al. 1992; Rodrigues et al. 1991; Shapiro et al. 1985; Stein and Aronson 1953; Tripathy 1987; Vandiviere et al. 1973).

The protective efficacy of BCG against TB has been evaluated by several meta-analyses (Brewer 2000; Colditz et al. 1994, 1995). For BCG vaccination during infancy, the summary protective efficacy was 65 % (95 % confidence interval (CI) 12–86 %) against death from TB, 64 % (95 % CI, 30–82 %) against TB meningitis, 78 % (95 % CI 58–88 %) against disseminated TB, 83 % (95 % CI 58–93 %) against

laboratory-confirmed TB, 74 % (95 % CI, 62–83 %) against any TB case when estimated from randomized controlled trials, and 52 % (95 % CI 38–64 %) against any TB case when estimated from case–control studies (Colditz et al. 1995). These findings corroborated summary protective effects of BCG against severe forms of TB demonstrated by another meta-analysis (Rodrigues et al. 1993): 86 % (95 % CI 65–95 %) against miliary or meningeal TB according to randomized controlled trials and 75 % (95 % CI 61–84 %) according to case–control studies.

Assuming that TB meningitis is approximately 1 % of the annual risk of infection, it has been estimated that every 12,500–16,667 BCG vaccinations during infancy will prevent one case of TB meningitis among children under 5 years (Fine et al. 1999). Assuming an annual risk of infection from 0.5 to 1 %, a risk of primary disease from 1 to 5 %, and that BCG vaccination in infancy confers 50 % protection against childhood TB, it has been estimated that 267–2667 vaccinations will prevent one case of childhood TB (Fine et al. 1999).

Observed findings regarding BCG efficacy may suggest that BCG is particularly effective in preventing hematogenous spread of *Mycobacterium tuberculosis* (Balasubramanian et al. 1994; Marsh et al. 1997), but not so efficient in preventing the establishment of lung infection following exposure (Sutherland and Lindgren 1979). However, there is increasing evidence from observational studies that BCG can also reduce the risk of infection (Diel et al. 2011; Eisenhut et al. 2009; Eriksen et al. 2010; Leung et al. 2015; Roy et al. 2014; Soysal et al. 2005) and aid bacillary clearance during treatment of pulmonary disease (Jeremiah et al. 2010).

Besides differences in methodology (Rieder 2008), a number of hypotheses have been proposed to explore the highly variable efficacy of BCG against pulmonary TB (Fine et al. 1999; Lambert et al. 2009; Rieder 2008). These include differences in the BCG vaccine, the virulence between *M. tuberculosis* strains, and the stages in the TB epidemic. There are also variations in host factors such as nutritional status, exposure to environmental mycobacteria, ultraviolet light exposure, and genetics underlying susceptibility. Table 20.1 summarizes the arguments for and against such hypotheses. Although there is still no consensus, partial protection conferred by environmental mycobacterial exposure may offer a biologically plausible explanation that partly addresses why BCG efficacy tends to be higher in temperate regions than tropical regions and, in particular, rural areas with greater exposure to environmental mycobacteria.

20.3.3 Efficacy of BCG Revaccination

In addition to neonatal BCG vaccination, many countries have a tradition of repeated BCG vaccination (Fine et al. 1999). Some administer multiple doses of BCG at infancy, school entry, and graduation, whereas some (as in Hungary and Russia) have recommended up to five doses of BCG from birth to 30 years of age. Although it is debatable whether the protective effect of BCG against pulmonary disease may last more than 15 years after vaccination (Sterne et al. 1998), studies in Malawi,

Table 20.1 Hypotheses regarding variable efficacy of BCG vaccination (Fine et al. 1999; Lambert et al. 2009; Rieder 2008)

Hypothesis	Arguments for	Arguments against
Differences in vaccine strains	BCG strains provided variable protection in the rabbit (Dannenberg et al. 2000) and guinea pig models (Smith et al. 1979). Based on animal studies of immunogenicity, Pasteur-1173 P2 and Copenhagen-1331 have been labeled "strong" and Glaxo-1077 and Tokyo-172 "weak"	The Chingleput trial showed that neither the Pasteur nor the Copenhagen strain was efficacious (WHO 1979; Indian Council of Medical Research (ICMR) 1999; Baily 1980)
		Shift from Japan and Glaxo to Paris and Danish vaccines in Indonesia and Columbia suggested that the Pasteur and Copenhagen vaccines might be less protective (Comstock 1988), but another trial in Hong Kong suggested that the Pasteur vaccine might be more protective than the Glaxo vaccine (ten Dam 1993)
Differences in vaccine doses	Variable doses given by multipuncture devices might have variable BCG doses, thereby leading to variable efficacy of BCG in trials involving multipuncture administration (Bettag et al. 1964; Comstock and Webster 1969; Frimodt-Moller et al. 1973; Rosenthal et al. 1961)	The Chingleput trial demonstrated no difference in BCG efficacy between two doses with 10-fold difference (Baily 1980)
Different exposure to environmental mycobacteria	In guinea pig TB models, exposure to different environmental mycobacteria and BCG conferred variable protection (Palmer and Long 1966)	Not all findings are consistent with masking of BCG protection by environmental mycobacteria (Fine 1995)
	In murine TB models, airborne infection with *M. avium* complex conferred similar protection against TB as the Danish BCG strain (Orme and Collins 1984)	
	In murine TB models, timing of exposure to *M. vaccae* before BCG affected sensitization by BCG (Brown et al. 1985)	
	Exposure to environmental mycobacteria might partly explain why BCG given earlier in life afforded larger protection in the Chingleput trial (Indian Council of Medical Research (ICMR) 1999)	
	In Puerto Rico, BCG conferred less protection in rural areas with higher exposure to environmental mycobacteria (Comstock and Edwards 1972)	
	There may be higher exposure to environmental mycobacteria in tropical regions. The protective efficacy of BCG against pulmonary TB in children is generally lower in tropical than temperate regions (Colditz et al. 1995; Putrali et al. 1983; Shapiro et al. 1985; Tripathy 1987)	

Difference in ultraviolet light exposure	The sensitivity of BCG bacilli and dermal Langerhans cells to UV may partly explain a tendency for lower protection in tropical regions (Fine 1995; Wilson et al. 1995)	This does not explain why BCG has conferred more protection against leprosy than TB in the same population (Pönnighaus et al. 1992; Tripathy 1983)
Genetic differences underlying host susceptibility	Vitamin D receptor, interferon receptor polymorphisms, NRAMP, HLA-DR, HLA-DQ, and other genes that control immune mechanisms influence susceptibility to TB (Bellamy et al. 1998; Brahmajothi et al. 1991; Goldfeld et al. 1998; Jouanguy et al. 1996, 1997; Khor et al. 2010). Thus, different genetic makeups may partly account for the variable efficacy of BCG	None yet published
Nutritional differences between study populations	Poor nutritional status is expected to impair cellular immune mechanism and hence the protective efficacy of BCG (Rieder 2008)	BCG conferred high levels of protection among poorly nourished native American children than well-nourished British adolescent (Hart and Sutherland 1977)
		This does not explain why BCG has conferred more protection against leprosy than TB in the same population (Pönnighaus et al. 1992; Tripathy 1983)
Difference in virulence between *M. tuberculosis* strains	Assuming that less virulent strains can confer protection against TB but induce false-negative tuberculin skin test, the protective effect of BCG vaccination among infected but tuberculin-negative subjects is masked (Rieder 2008)	Masking of protective effect is likely incomplete, but some BCG trials have demonstrated no protection at all (Rieder 2008)
Different stages in the TB epidemic	Assuming that the protective effect of BCG is masked by primary infection and exogenous reinfection, BCG is expected to offer less protection in places with higher risk of TB infection (Smith et al. 2000; ten Dam and Pio 1982)	Despite a declining risk of infection in the UK, BCG still conferred a persistently high level of protection (Rodrigues et al. 1991)

Brazil, Chile, Hong Kong, and other countries have suggested the lack of additional protection from BCG boosters (Karonga Prevention Trial Group 1996; Dantas et al. 2006; Rodrigues et al. 2005; Sepulveda et al. 1992; Springett and Sutherland 1994; Tala-Heikkilä et al. 1998). Over 30 countries have ceased BCG revaccination, whereas 16 still administer BCG boosters (Zwerling et al. 2011). A lack of additional protection from BCG revaccination may be partly explained by a diluting effect from continuous exposure to TB and environmental mycobacteria (Fine 1995).

20.3.4 Efficacy of BCG Vaccination Among Healthcare Workers (HCW)

It is contentious whether BCG may confer appreciable protection against TB among HCW. Assuming a workplace incidence of TB infection greater than 0.06 % per year, a decision analysis involving tuberculin-negative HCW showed that treatment of LTBI decreased the number of TB cases by 9 %, whereas BCG vaccination decreased the number by 49 % (Marcus et al. 1997). Another decision analysis among HCW exposed to multidrug-resistant TB (MDR-TB) also suggested that BCG was beneficial (Stevens and Daniel 1996). However, a review by Brewer and Colditz (1995) suggested that methodological flaws in the published literature would preclude a meta-analysis of efficacy of BCG among HCW. The United States CDC has suggested that BCG be considered among tuberculin-negative HCW when there is a high risk of exposure to multidrug-resistant TB and the risk cannot be effectively contained by comprehensive TB infection control measures (CDC 1997).

20.3.5 Efficacy of BCG Against Other Mycobacterial Diseases

BCG has been shown to confer protection against leprosy (Abel et al. 1990; Brown et al. 1968; Fine 1988; Fine et al. 1986; Lwin et al. 1985). The cessation of BCG vaccination was followed by a higher incidence of peripheral lymphadenitis due to environmental mycobacteria in Sweden (Romanus et al. 1995) and *M. avium* in the Czech Republic (Trnka et al. 1994). It has been postulated that infection with one species of mycobacterium triggers a cellular immune response that acts more swiftly in killing other mycobacteria subsequently encountered.

20.4 Need for Better Vaccines

BCG is insufficient for protecting against pulmonary TB, which contributes to the main public health burden of TB. A highly efficacious vaccine may be required for improving TB treatment efficacy and combating drug-resistant TB. HIV infection

has fuelled the TB epidemic. Matched case–control studies suggest that HIV infection may abrogate the protective effect of BCG against extrapulmonary TB (Arbeláez et al. 2000). A safer and more effective TB vaccine is needed for HIV-infected subjects.

Four types of candidate TB vaccines have been proposed on the basis of a comprehensive TB vaccination strategy (Lambert et al. 2009): (1) a priming vaccine that induces the host immunity in preparation for subsequent boosters, (2) a boosting vaccine that enhances the immunity induced by the priming vaccine, (3) a vaccine for postexposure administration among healthy adolescents or adults, and (4) a therapeutic vaccine that can increase TB treatment efficacy or shorten TB treatment duration.

Reflecting new approaches in vaccinology, candidate TB vaccines can be classified into several categories (Lambert et al. 2009): (1) live attenuated vaccines (such as recombinant or recombinant attenuated *M. tuberculosis*), (2) live vectored subunits (such as adenovirus or Modified Vaccinia Ankara), (3) recombinant proteins in adjuvants, (4) DNA vaccines, and (5) whole-cell killed mycobacteria (such as *M. vaccae*).

Without safer and more effective vaccines alongside better tools for the diagnosis and treatment of TB, it may be difficult to meet the Millennium Development Goals of halving the global TB prevalence and death rates by 2015 relative to their levels in 1990 and eliminating TB as a public health problem by 2050 (WHO 2010a). Modeling studies have demonstrated that neonatal vaccination with a preexposure vaccine that is 60 % effective would reduce 39 % of the TB incidence by 2050 in southern Asia (Abu-Raddad et al. 2009). The same model shows that mass vaccination with such a preexposure vaccine can achieve a much bigger impact on TB transmission and prevent 84 % new cases (85.9 million) and 81 % deaths (14.5 million) (Abu-Raddad et al. 2009).

By April 2009, the development pipeline for TB vaccines had included seven candidates tested in humans, including two nonreplicating viral-vectored vaccines in Phase IIb trial in infants and in HIV-infected adults (Beresford and Sadoff 2010). By the end of 2010, 10 vaccine candidates had entered different phases of trials (5 in Phase I, 2 in Phase II, 2 in Phase IIb, and 1 in Phase III trials) (WHO 2010a). By August 2014, a total of 15 vaccine candidates were in clinical trials, including recombinant BCGs, attenuated *M. tuberculosis* strains, recombinant viral-vectored platforms, protein/adjuvant combinations, and mycobacterial extracts (WHO 2014).

20.5 Future Perspectives

TB vaccine development is onerous and challenging. Although the deciphering of the whole genome of *M. tuberculosis* (Cole et al. 1998) and the significant progress on sequencing that of BCG have facilitated the development of better vaccines, it is by no means easy to evaluate the efficacy of new vaccines in developing countries in the presence of confounding factors that can boost the host immunity, such as TB disease, BCG vaccination, and environmental mycobacteria.

Major obstacles include (1) major gaps in scientific knowledge: inadequate understanding of natural host immunity and bacillary latency, the lack of surrogate markers for vaccine-induced immunity in humans, and a dearth of more natural nonhuman primate models of TB infection; (2) underfunding of expensive TB research work; and (3) the need for sustained political commitment in making future vaccines affordable, accessible, and available in areas that need them most (Beresford and Sadoff 2010).

Science alone is inadequate for combating TB (Beresford and Sadoff 2010; Migliori et al. 2007). Concerted efforts are required to integrate scientific advancement and political mobilization to ensure that substantial TB-related morbidity and mortality can be effectively avoided by mass vaccination campaigns using better TB vaccines.

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Chapter 21
Latent Infection with *Mycobacterium tuberculosis*

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21.1 Latent Infection with *Mycobacterium tuberculosis*

M. tuberculosis has been thought to appear in two distinct stages in the human host: active TB disease (referred to as "tuberculosis") and latent infection. Persons who are close to and exposed to infectious TB patients are at risk of being infected by *M. tuberculosis.* The risk of infection is higher among those who are exposed to sputum smear-positive (as compared with smear-negative) TB patients, those who are exposed to coughing patients, those who are exposed in poorly ventilated areas, and those who have a long duration of such exposure. The probability of infection is probably also associated with the virulence of the TB bacilli. Among those who are infected with *M. tuberculosis*, a minority may soon progress to disease (primary TB), but the great majority manage to contain or eliminate TB bacilli by an effective immune response.

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21.1.1 *Latent Infection with* M. tuberculosis *as Distinguished from Active TB Disease*

Latent infection refers to a clinical state in which infection with TB bacilli has been established and contained in a human host so that the bacteria are not actively reproducing. There is neither clinical nor bacteriological evidence of disease. Latent infection may remain clinically silent and unrecognized for life or for a prolonged period of time and then subsequently activated into clinical disease.

21.1.2 *Evidence of Latent Infection with* M. tuberculosis

Pathology studies that recovered viable TB bacilli from subjects without clinical signs of TB have provided evidence of latent infection with *M. tuberculosis* (Stewart et al. 2003). A molecular epidemiological study in Denmark demonstrated that endogenous reactivation of *M. tuberculosis* can occur after 33 years of latent infection. A man who developed TB in 1994 was infected with strains that had identical DNA patterns with isolates from his father who had developed TB in 1961; there were no other strains that shared the same DNA pattern in the collection of 4008 clinical strains in Denmark (Lillebaek et al. 2002). A polymerase chain reaction study done on normal lung tissues from Ethiopian and Mexican individuals who had no TB lesions revealed that *M. tuberculosis* DNA was situated in macrophages, type II pneumocytes, endothelial cells, and fibroblasts (Hernández-Pando et al. 2000). To date there is no single clinical tool that can unambiguously identify the presence of latent infection with *M. tuberculosis*.

21.2 Diagnosis of Latent Infection with *M. tuberculosis*

For decades, the immunological response in the host to mycobacteria detected by the tuberculin skin test has been used as a proxy for latent infection with *M. tuberculosis* and recently also by the newly developed IGRAs.

21.2.1 *Tuberculin Skin Test*

Tuberculin was obtained from a broth culture filtrate of TB bacilli initially developed by Robert Koch as a potential treatment of TB (Koch 1890). While not successful as a treatment, Koch recognized tuberculin as a potential tool in the diagnosis of infection with *M. tuberculosis*. Purified protein derivative (PPD) of tuberculin prepared by Florence Seibert was recommended by the World Health

Organization (WHO) as the international standard (PPD-S) for tuberculin. The most commonly used tuberculin is PPD RT-23 produced in Copenhagen, Denmark. The standard Mantoux method of skin test involves intradermal injection of PPD, and reactions are determined by measuring the transverse diameter of the induration after 48–72 h. It was demonstrated that 2 tuberculin unit (TU) PPD RT-23 is equivalent to 5 TU PPD-S (Menzies 2000). The reaction in response to the tuberculin skin test in persons infected with *M. tuberculosis* (e.g., a group of TB patients) is normally distributed with a median at approximately 17 mm and a distribution that may extend from just around 5 mm to just over 25 mm. The natural immunological responses, as well as nonspecific sensitization to environmental mycobacteria and BCG vaccination, influence the results of the tuberculin skin test by a distribution of smaller size of induration. Therefore, the cutoff used to define a positive tuberculin skin test depends on circumstances in which the test is performed and intended use of the results. When used in an epidemiological study, the appropriate cutoff indicating a positive test depends on the distribution of the size of the reaction in the study population. A true distribution for latent infection with *M. tuberculosis* in the population may be derived from a frequency distribution of reactions among a group of bacteriologically positive TB patients from the same community. To estimate the prevalence of latent infection with *M. tuberculosis*, models of mixture analysis estimating underlying distribution have been applied in a limited number of settings (Rieder 2005). This model simultaneously examines two distributions within one set of data (one for *M. tuberculosis* and one for other Mycobacteria species). For preventive therapy, commonly used cutoff points for a positive test include 5 mm, 10 mm, and 15 mm induration depending on the characteristics of tested subjects. Selection of cutoff levels involves trade-offs between sensitivity and specificity in determining the possible presence of immune response to *M. tuberculosis*. Unfortunately, the tuberculin skin test is a blunt tool in predicting future risk of progression to active TB. Among those who are not infected with HIV, the estimated risk of TB of those with a positive skin test is 10 % in a lifetime (Styblo 1991), highest soon after infection and falling exponentially with time.

21.2.2 Interferon-γ Release Assays

Interferon-γ release assays (IGRAs) have been developed to diagnose infection with *M. tuberculosis*. They are in vitro immunological tests that detect T-cell immune response against *M. tuberculosis*-complex antigens, including the early secretory antigenic target (ESAT)-6, culture filtrate protein (CFP)-10 and/or TB7.7. These antigens are not expressed by the majority of environmental mycobacteria; exceptions are *Mycobacterium kansasii*, *Mycobacterium szulgai*, and *Mycobacterium marinum* (Andersen et al. 2000). The positive reactions due to these organisms are inversely related to the prevalence of *M. tuberculosis*. They also vary to some extent by geographical location. Consequently, they may explain a high proportion of positive tests in a location such as the South Eastern United States. There are two

commercially available IGRAs: QuantiFERON-TB Gold In-tube (QFT-GIT; Cellesis, Carnegie, Australia) and T-SPOT.TB (Oxford Immunotec, Abingdon, UK). Both IGRAs and tuberculin skin tests are measuring adaptive immune response (Mack et al. 2009) against *M. tuberculosis* but in different manners; it is common to find discordant results between IGRAs and tuberculin skin tests. There is no gold standard for detection of latent *M. tuberculosis* infection. IGRA sensitivity for this use is commonly assessed using subjects with microbiologically confirmed TB; the specificity is assessed using healthy individuals with no known exposure to TB in low TB prevalence settings. It has been reported that, while specificity of the tuberculin skin test is affected by BCG vaccination, IGRAs have a high specificity among both BCG-vaccinated and BCG-unvaccinated populations and that sensitivity of IGRAs is comparable to the tuberculin skin test but varies across study populations (Pai et al. 2008). Further, the risk of IGRA positivity is clearly associated with exposure to contagious TB cases (Diel et al. 2011a).

One of the key questions concerning the utility of IGRAs is their ability to predict future risk of developing TB. For studies performed in low incidence settings, pooled negative predictive value for the risk of progression to TB within 2 years in immunocompetent adults was 97.8 % for T-SPOT.TB and 99.8 % for QFT-GIT (Diel et al. 2011a, b). Positive predictive value for the risk of progression to TB within 2 years among those who had positive test results of tuberculin skin test was 2.3–3.3 % and varied substantially for IGRAs, ranging from 2.8 to 14.3 % for QFT-GIT and from 3.3 to 10 % for T-SPOT.TB (Diel et al. 2011a, b). These data need to be interpreted with caution because these tests were evaluated in different study populations where the prevalence of latent infection varied.

21.3 Risk and Distribution of Latent Infection in a Population

The risk of infection with *M. tuberculosis* in a given population can be measured by counting the number of persons newly infected (or reinfected) with TB in a given period in time (usually in a year). Direct measurement of the risk of infection requires testing a group of persons repeatedly to see how many of those who are negative become positive after a given period in time, which is complicated to do and needs a large sample size. Risk of infection is usually estimated by measuring the prevalence of infection in a birth cohort at a given age (Styblo 1991). Average annual risk of infection, resulting in the observed prevalence of infection, is calculated on the basis of probability of not being infected in each calendar year between the birth year of the cohort and the year of the survey, the estimate centered on a year equivalent to one-half the age of the group tested. Consequently, the average annual risk of infection derived for a group of children aged 12 years, tested in 2006, is the risk of infection for the year 2000. That is, the test result is a cumulative estimate of the probability of having become infected over the current age (and time period of life) of the child tested.

In a given population, the prevalence of latent infection with *M. tuberculosis* (shown by positive tuberculin test results) usually increases with age, is higher among males than females, and varies by socioeconomic determinants. The annual risk of infection in Europe was very high in the early twentieth century, estimated as high as 10 % in the Netherlands in 1910 (Styblo et al. 1969). A rapid decline in the risk of infection in Europe was associated with a substantial reduction in TB case notification. Currently, a high proportion of the elderly in Europe remain latently infected with *M. tuberculosis* due to a high risk of infection in the past, but among the younger generation, the proportion infected is very low. The annual risk of infection in low-income countries in the late twentieth century was not as high as that in early twentieth century Europe, but the annual decline of risk of infection has been relatively low (Cauthen et al. 1988). This implies that a relatively high proportion of the younger generation is still continuously exposed to sources of transmission and/or has been infected.

The risk of infection is related to not only the number of TB patients in a community but also the duration of infectiousness of these cases. Inadequate treatment of TB may prolong the duration of infectiousness of TB cases and generates a negative impact on the control of epidemics. Tuberculous infection does not confer complete protection against reinfection (Chiang and Riley 2005). Persons previously infected with TB remain at risk of reinfection with TB. However, once infected, there is no test to differentiate between a primary tuberculous infection and a subsequent reinfection.

21.4 Risk Factors Associated with Progression to Active TB Disease

Once a patient is infected, the risk of progression to active TB disease is largely determined by the ability of the immune system to contain or eliminate TB bacilli. Children under 5 years of age (and particularly infants under 2) have a higher risk of progression because of immaturity of the immune system. HIV is a strong risk factor for the rapid progression of recent infection and reactivation of remote latent infection. Other risk factors of active TB disease include recent infection, healed TB (e.g., fibrotic lesions) that was not previously treated, immunosuppressive therapy (such as anti-TNF-α), diabetes mellitus, renal failure, silicosis, malnutrition, tobacco smoking, excessive alcohol intake, genetic factors (NRAMP gene), and the anatomical shape of the tracheobronchial tree (especially in tall thin persons), as well as socioeconomic factors (Lienhardt 2001). Exposure to combustion of solid fuels (indoor air pollution, IAP) has been listed as a potential risk factor but the evidence supporting such an association is conflicting (Lin et al. 2014). The impact of a risk factor on the epidemic of TB in a population is determined by the relative strength of association between the risk factor and TB, the prevalence of the risk factor, and the extent of overlap between the subpopulation with the risk factor and the subpopulation latently infected with *M. tuberculosis*. As the prevalence of HIV is

relatively high in sub-Saharan Africa and relatively low in Asia, HIV has been the driving force of the epidemic of TB in (e.g.) Kenya, Tanzania, South Africa, and Zimbabwe but may not have had a significant influence on the epidemic of TB in China, India, and Indonesia (Lönnroth et al. 2010). In contrast, smoking has a much bigger impact on the epidemic of TB in these countries because smoking is so common.

21.5 Strategies for Reducing Risk of Infection and Progression from Latent Infection to Active Disease

Latent infection with *M. tuberculosis* in the human host constitutes the fundamental challenge of TB control because new TB cases will continuously arise from the pool of persons already infected. The core principle of the modern TB control strategy is to reduce the risk of transmission and foster an infection-free generation.

21.5.1 Intensified Case Finding and Effective Case Management

To reduce the risk of transmission of *M. tuberculosis* from TB patients to healthy individuals, it is crucial to efficiently identify infectious TB cases, especially smear-positive cases, and render them noninfectious by effective chemotherapy and case management. Proper decentralization of TB services to a level which is accessible by the majority of the population helps reduce patient delay in seeking healthcare. Well-trained health personnel capable of timely identification of TB suspects for diagnostic examination would reduce health system delay. Efficient enrollment of all detected cases into treatment is another crucial step. All infectious TB cases diagnosed should be treated following international recommendations of directly observed therapy with every effort to ensure adherence. Carefully designed active case finding among groups at a high risk of developing TB may complement facility-based services in reducing transmission (Corbett et al. 2010). Inadequate treatment prolongs the duration of infectiousness, facilitates transmission, and runs the risk of generating drug-resistant TB.

21.5.2 Infection Control in Hospital and Congregate Settings

The risk of infection is particularly high in healthcare facilities, prisons, and congregate residential facilities if infection control is inadequate. Very large nosocomial outbreaks of multidrug-resistant TB have been recorded in healthcare institutions in

low-income countries, especially in areas with a high rate of HIV infection, with rapid progression of disease and death of those affected. Measures for control of infection in institutions and congregate settings can be complex and very costly. However, there is a hierarchy of measures that can guide managers in ensuring increasingly effective infection control in these settings. This begins with the so-called "fast tracking": rapid identification of those most likely to be highly infectious and immediate testing to identify such cases. This is especially important in settings where there is a congregation of clients with suppressed immune systems (infants, those infected with HIV, those on treatment with immunosuppressive therapy, etc.). A second essential element is ensuring the best possible ventilation in congregate settings, which can involve simple matters such as opening windows and arranging the logical layout of healthcare facilities to ensure that the air and the patients move in such a way that the flow is from potential source cases to the exterior rather than to other clients or staff. These are the most basic elements of infection control that need to be ensured before other and more sophisticated and expensive measures are put into place.

21.5.3 Reducing the Risk of Progression from Latent to Active TB

There are two potential strategies for reducing the impact of risk factors on the epidemic of TB: reducing the prevalence of risk factors and reducing the strength of their impact. In Africa, it is not possible to control TB without controlling HIV (Dye et al. 2005). The recent decline of the epidemic of HIV will offer a better chance of TB control (Mansoer et al. 2009). Among those who are already infected with HIV, highly active antiretroviral therapy (HAART) can substantially reduce the risk of progression to TB (Badri et al. 2002). Smoking has been convincingly shown to be associated with TB (Slama et al. 2007). Implementation of the Framework Convention of Tobacco Control to reduce the prevalence of smoking would benefit TB control, as smoking cessation may potentially reduce the risk of progression to TB (Wen et al. 2010). Likewise, proper glycemic control in patients with diabetes mellitus, an emerging epidemic in many countries, may reduce the risk of TB (Leung et al. 2008).

21.5.3.1 Preventive Chemotherapy

It has been clearly shown that isoniazid preventive chemotherapy (IPT) using isoniazid for 6–12 months reduces the risk of progression to active TB. Other regimens include isoniazid and rifampin for 3 months, or rifampin for 4 months (Leung et al. 2011). However, failure to exclude subjects with active TB runs the risk of generating isoniazid-resistant TB. Preventive chemotherapy has not been widely used at

population level, partly because it is difficult to ensure adherence among healthy clients who are asymptomatic. Among persons living with HIV, IPT alone does not have a long-lasting effect (Quigley et al. 2001) and must be implemented together with HAART (Golub et al. 2009). Moreover, the effect of IPT may not be sustainable in settings where the risk of infection remains high because the individuals remain at high risk of reinfection.

21.6 Prospects of TB Control

The current global TB control strategy focusing on diagnosis and treatment of active tuberculosis cases is unlikely to achieve the goal of elimination of TB in the near future (Dye et al. 2013). A strategy to effectively address TB arising from the large pool of subjects latently infected with *M. tuberculosis* is essential. The physiological status of clients with latent infections is probably not homogenous, and further scientific research is required to clarify this variation (Barry et al. 2009). A vaccine-based approach consisting of preexposure vaccine (preventing infection) and post-exposure vaccine (preventing progression to disease) may have a substantial impact on TB control (Young and Dye 2006). The risk of progression among IGRA-positive persons remains relatively low (Diel et al. 2011a, b). A new tool, or novel use of IGRAs that can better predict disease progression among those latently infected, will improve the effectiveness of preventive therapy (Andersen et al. 2007). Finally, adherence to treatment is difficult to ensure when the treatment of latent infection with *M. tuberculosis* needs to be applied for a prolonged period. The use of a 12-dose weekly rifapentine and isoniazid regimen might be helpful to ensure adherence but directly observed therapy will be required (Sterling et al. 2011). New drugs that can quickly kill TB bacilli in latent stage are needed (Andersen et al. 2007).

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Chapter 22
The Tuberculosis Outbreak Response, Investigation, and Control

Robert E. Fontaine

22.1 Introduction

Tuberculosis (TB) outbreaks can sometimes reveal unanticipated factors which require modifications of control approaches. For example, in New York City in the 1980s, TB incidence was rising despite ongoing control. Inadequate resources were part of the problem (Brudney and Dobkin 1991). A series of outbreak investigations provided in-depth understanding of three additional factors: the emergence of multidrug-resistant TB (Centers for Disease Control and Prevention (CDC) 1991a), TB in HIV-infected persons (Brudney and Dobkin 1991), and transmission in hospitals (CDC 1991a; Frieden et al. 1996). As in New York, outbreak investigation in other areas may reveal important keys to solving difficult problems with TB control programs.

22.2 Special Characteristics of TB Outbreaks and Their Implications

Several key characteristics of TB limit the potential pathways and situations for transmission and thereby simplify the approach to TB outbreaks. The mode of transmission, exclusively airborne, is known from the beginning. TB outbreaks, with rare exceptions, involve exposure of susceptible individuals to a person or

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persons with active pulmonary disease or less commonly laryngeal infection. Through coughing, singing, sneezing, shouting, or similar forceful expulsion of air they create aerosols of suspended infectious particles (Buff and Raviglione 2008). Thus, the most critical element of outbreak investigations is the complete and intensive identification of active pulmonary TB cases in groups or networks of persons involved in outbreaks.

TB outbreaks develop slowly. After an exposure, the minimum incubation period for development of new pulmonary TB disease is approximately 6 months. New cases of pulmonary disease among exposed persons will concentrate over the 2 years following exposure (Buff and Raviglione 2008). Additional TB disease will appear; about 10 % of exposed persons will develop TB disease over their lifetime (Buff and Raviglione 2008). Thus, recognizing TB outbreaks requires a very good case finding, a high level of suspicion, attention to latent infections, and patience.

Exposure of a group of individuals to TB will result in many new latent infections. During outbreak investigations, the epidemiologic assessment of these latent infections, because they far outnumber and precede cases of active pulmonary and extrapulmonary TB, is critical to identifying groups at higher risk and understanding transmission patterns during outbreaks. Since each latent infection has a 10 % probability of developing into TB disease over the lifetime of the infected individual, identification and treatment of latent TB during outbreaks will always be an important control measure.

22.3 What Is an Outbreak?

An outbreak or epidemic is any increase in the number of cases of a disease above the anticipated level for a population or group. With diseases under public health surveillance, such as TB, these increases will be detectable through regular review of surveillance data. New TB cases in an administrative unit during a defined period of time are compared to an expected level. This expected level is estimated from the surveillance data for the preceding years for the same time period in the same population.

Prevention and control programs should and often do have specific targets for progressive decreases in incidence and prevalence. Epidemiologists should pay attention to these targets and estimate epidemic levels with the expectation of a decrease in TB according to these targets. In this environment (e.g., with a control program in place), an outbreak or epidemic definition can be extended to any unexpected increase above the projected level for the control program for that particular population group, place, or time. Whether the situation is called an outbreak or not, identifying the reasons underlying these program failures and correcting them will follow the same steps as an outbreak or epidemic investigation.

Effective detection of TB outbreaks depends upon the quality of the TB surveillance system. Timeliness, sensitivity, and specificity of the surveillance system are critical. Timeliness, reflected by early diagnosis and notification of new TB cases

combined with frequent review of accumulated data, allows epidemiologists to begin investigations and mount control activities before the TB transmission gets out of hand. A TB case definition that is applied consistently over extended time periods (decades) and across all geographic areas of a country or administrative units is essential in maintaining specificity and sensitivity of surveillance. For outbreak detection purposes, a high proportion of laboratory confirmed cases will allow outbreak signals in the surveillance data to appear earliest and in the smallest groups of people. Lack of interference of the background of "clinically diagnosed" cases of unknown specificity will also make laboratory-based surveillance efficient at separating smaller, relevant increases or deviations from expected endemic levels. Outbreak detection can similarly be enhanced using genotyping that will distinguish clusters or increases in a specific genotype of *Mycobacterium tuberculosis* from the background of all other genotypes (Dobbs et al. 2001; Fitzpatrick et al. 2001; Malakmadze et al. 2005; McNabb et al. 2004).

Determination of baseline levels, and projections of future declines expected from control and prevention measures, is fundamental to outbreak detection. These expected levels are normally computed from past data. In their simplest form, these are averages (means or medians) or totals of new TB cases from the same period of the preceding years. The new cases for the current period are then compared to these expected estimates. For example, one could compare the current number of TB cases from April to June to the median of the totals from the April to June period for the preceding 5 years. Since TB has a highly variable onset relative to exposure, using the date of report or diagnosis has no practical disadvantages compared to date of onset. Simple line graphs which compare the current case numbers against past averages can facilitate detection of unexpected increases.

Two modifications of this basic approach will improve early detection. First, one can include desired decreases from control activities in the expected projections. Consider a control program with a target of a 5 % decrease in new TB cases each year. If the program has just started and the median for the preceding 5 years was 100 cases, then the expected number should be 95 cases. However, if the control program has been ongoing for the entire 5 years, one should assume that a 5 % decrease occurred consecutively over the 3 years from the midpoint of that 5-year reference period. Thus, the expected level in the current year would be 100(.95)(.95)(.95) = 86 cases. Second, one may estimate expected levels for smaller, high-risk groups from rates in larger population units. To do this, one needs to calculate incidence rates for a large administrative area or group such as a province, provincial wide school system, and healthcare system. These incidence rates may be multiplied times the population of the smaller units within the larger area such as a county, individual school, or group of schools. This approach provides target levels for population units which individually have background case numbers which are too small to make reliable estimates. Note that this exercise will also help identify population groups that, as a whole, have not met program targets and could be considered to have epidemic TB.

Since TB transmission characteristically occurs from close exposure within enclosed spaces, outbreaks, or clusters commonly appear where groups of people

gather together for prolonged periods for joint activities. These situations could include schools, child care facilities, workplaces, ships, places of worship, military barracks, etc. (Reves et al. 1981; Sacks et al. 1985; DiStasio and Trump 1990; Binkin et al. 1993; Dutt et al. 1995; Ridzon et al. 1997; Mangura et al. 1998; Calder et al. 2000; Cook et al. 2000; Lamar and Malakooti 2003; Phillips et al. 2004; Dewan et al. 2006; Stein-Zamir et al. 2006; Duthie et al. 2008; Gillman et al. 2008). In some situations, the involved populations have a higher probability of having an individual with TB and also a higher proportion of persons with risk factors for acquiring TB. These include prisons, homeless shelters, chronic care institutions, hospitals, etc. (Giovanni et al. 1989; Haley et al. 1989; CDC 1991b, 1993, 2000, 2004; Nolan et al. 1991; Daley et al. 1992; Luby et al. 1994; Valway et al. 1994; Ikeda et al. 1995; Zaza et al. 1995; Frieden, et al. 1996; Bergmire-Sweat et al. 1996; Agerton et al. 1997; Haas et al. 1998; Nivin et al. 1998; Curtis et al. 2000; Kearns et al. 2000; Díaz et al. 2001; Hannan et al. 2001; Ijaz et al. 2002; Freeman et al. 2005; Macaraig et al. 2006; Huang et al. 2007; Sosa et al. 2008). Often the staff or management of these settings note the appearance of a cluster of new TB patients and report them to the public health department or TB program. The public health department then determines, through contact tracing and case finding, if more cases are linked to the cluster and if an outbreak exists.

22.4 Application of TB Diagnostic Tools During Outbreak Response

TB outbreak response and investigation utilize the same diagnostic tools used during TB control. These include the tuberculin skin test (TST) and interferon-gamma release assay (IGRA) to detect latent infection (Mazurek, et al. 2010), sputum smear for acid fast bacilli and sputum culture for *M. tuberculosis* to detect active TB disease, detection of antimicrobial sensitivity on *M. tuberculosis* isolates for determining drug regimens, and genotyping of *M. tuberculosis* isolates to show relationships between isolates. These tests may have special applications and interpretations during outbreak response.

Detection of new infections is particularly important during outbreaks. Individuals with recent infections have much more precise information about their exposure. In addition, new infections are much more likely to appear as pulmonary disease over the 2 years following exposure. These individuals are thus an important target for chemoprophylaxis for outbreak control.

The TST or IGRA does not differentiate between infection, new latent infection, and chronic latent infection. There is a delay of 2–6 weeks from the initial infectious exposure to development of a positive test (Buff and Raviglione 2008). Accordingly, during outbreaks persons who initially have negative or low reactivity should have repeat tests 6 weeks after the first test (or later if source cases are not quickly detected). IGRA retesting may need to be done up to 10 weeks after the negative test

(Mazurek, et al. 2010). A major change in the area of induration of a TST (e.g., from zero to above 5 mm or from a small area to a large area of induration) can be interpreted as new infection. Unlike TST, IGRA does not induce boosting and should give more definitive results in retesting during outbreaks (Mazurek, et al. 2010). If the group has been previously screened with TST or IGRA, these prior results may be compared to the new results to determine recent infection.

Appearance of sputum or culture positive pulmonary TB among individuals involved in an outbreak can, for practical investigative purposes, be considered to be recently acquired rather than reactivation TB. Individuals with underlying risk factors for reactivation may require some additional assessment in this interpretation. Although cases with reactivation provide little information regarding transmission during the investigation, they may represent sources of TB and will require treatment.

Characterization of strains through genotyping or drug resistance patterns is of great assistance in outbreak investigations. This is particularly so in outbreaks which are dispersed throughout larger populations or social networks with no common living quarters, workplace, or school. With genotyping, cases may be linked together and evaluated as a common outbreak and additional outbreak-related cases may be detected through screening of isolates at hospital and TB laboratories (Kline et al. 1995; Kiers et al. 1997; Bock et al. 1998; Sterling et al. 2000a, b; Fitzpatrick et al. 2001; Klovdahl et al. 2001; McElroy et al. 2002; Ruddy et al. 2004; Freeman et al. 2005; Gardy et al. 2011).

22.5 A Stepwise Approach to TB Outbreak Response and Investigation

Both the initial control of outbreaks and the epidemiologic investigation may be best described following the 15 steps of the outbreak investigation (see Box 1). These have been adapted for TB from the more general 13 steps of an outbreak investigation as developed by the United States Centers for Disease Control and Prevention and detailed in Dicker et al. (2006).

22.5.1 Prepare for the Fieldwork

Once it is decided from review of existing data that an outbreak exists and requires investigation, one must anticipate and prepare for important needs. Diagnostics will be critical. All responses to TB outbreaks will require sufficient supplies to apply and read TST or IGRA on the entire group involved. Arrangements need to be made to have an initial supply of these materials at the site and to have additional supplies in reserve. Depending upon the situation and the availability of a local laboratory,

Box 1: The 15 Steps in Investigation of a TB Outbreak

Investigation of a TB Outbreak
1. Prepare for field work
2. Establish the existence of an outbreak
3. Verify the diagnosis
4. Construct a working case definition
5. Find cases systematically and record information
6. Assess application of standard control measures
7. Apply standard control measures
8. Perform descriptive epidemiology
9. Develop hypotheses
10. Evaluate hypotheses epidemiologically
11. Reconsider, refine, and reevaluate hypotheses as necessary
12. Compare and reconcile with laboratory and/or environmental studies
13. Implement control and prevention measures
14. Initiate or maintain surveillance
15. Communicate findings

Adapted from Dicker et al. (2006)

supplies for obtaining and staining sputum smears and for culturing sputum will be needed. One should consider including a microbiologist on the investigation team to manage all laboratory-related facets of the investigation. Personal protective equipment should be available for individuals who will work with patient specimens and cultures or who may be exposed to TB patients.

Administratively, one should ensure that all members of the team are freed from responsibility from their routine activities for the anticipated length of the investigation. This could involve anywhere from 1 to 4 weeks depending upon the scope of the problem. Individuals with conflicts during this time, whether personal or work related, should be replaced with others. Appropriate approval from local authorities is also necessary. In addition to the local health administration, the managers of the groups or institutions affected by the TB outbreak (e.g., school, prison, and factory) must be informed and prepared to cooperate fully. Lines and frequency of communication to health and other authorities need to be established.

22.5.2 Establish the Existence of an Outbreak

As discussed earlier, under a functioning TB surveillance system, systematic review of surveillance data is sufficient to determine if an outbreak or epidemic exists. Under these systems, increases in confirmed TB can result from improvements in detection of suspect cases and testing for TB (TST or IGRA, sputum smears, and

culture). When such improvements have been made, their effect should be assessed quantitatively to determine whether improved case detection or a true increase in infection (or both) are responsible for the case numbers.

Investigations may involve clusters of TB. A cluster is an aggregation of TB in a limited population which does not represent a significant increase above the expected level. It does provoke concern among the persons involved. Since TB outbreaks develop slowly, the cluster may represent an outbreak in early development. Since the principal measure for control is case finding and treatment, the early steps in an outbreak investigation, which follow, may also be applied to clusters.

22.5.3 Verify the Diagnosis

One should always confirm that the diagnosis of TB on individual cases was correct. Immediately upon arriving at the field, a comparison of the clinical presentation and the laboratory results will be needed. Inconsistencies will point to the need for deeper evaluation of specimen collection and test methods (Shears et al. 1994; Cronin et al. 1998; Segal-Maurer et al. 1998; Bearman et al. 2002). One should also review the laboratory procedures to assure that sputum smears were correctly read and that cross-contamination of cultures in the laboratory has not occurred. If TST was initially used for diagnosis, the source, storage, and methodology for applying tuberculin and reading the test require review. Sometimes, a TB outbreak may be suspected in an area where sputum smear or culture is not available. In this situation, one must quickly and accurately confirm the diagnosis.

22.5.4 Construct a Working Case Definition

A case definition is a standard set of criteria to decide if an individual should be classified as having TB or not. Under TB surveillance systems, case definitions will have been already applied to the reported cases. During an outbreak investigation, additional refinement of the TB case definition will be necessary. One needs to begin with a broad sensitive case definition that will identify as many potential "suspected" cases as possible for additional evaluation. For example, for pulmonary TB, this "suspected case" definition could simply be a cough illness lasting more than 2 weeks and opacities on the chest radiograph. To this basic sensitive definition, one adds more specific criteria. For example, a "probable case" could be a suspected case with a TST greater or equal to 15 mm of induration. A confirmed case could be a suspected or probable case with acid fast bacilli on a sputum smear or isolation of *M. tuberculosis* by sputum culture. When the drug resistance pattern or genotyping is available, then one can restrict the case definition to a specific resistance pattern or genotype.

In investigations of TB outbreaks, one can also define latent TB using a similar staging system. For example, a suspect case of latent TB could be a TST from 5 to 9 mm of induration in a person without respiratory illness or radiographic evidence of active disease. A probable case could be a TST greater or equal to 10 mm of induration in a person without respiratory illness or radiographic evidence of active disease. If recent previous skin test information is available, one may use a conversion from prior negative to a positive to represent recent infection. Different TST cutoff values could be appropriate for different settings with different levels of endemic TB infection. However, for the suspected case definition, it is usually better to err on the side of greater sensitivity. IGRA presents less uncertainty than TST; nevertheless, one could apply at least a two level definition using a low titer and higher titer.

For outbreak investigations, the case definition should always include: the time interval for which one is investigating, the place, and any specific characteristics of the population under investigation. Using the suspect case definition above, one would add, for example, the onset from January to June 2010 and a student or employee of University X. On the other hand, one should not include exposures or risk factors that one intends to assess during the investigation. For example, do not include in the case definition: "in a family, friend, or other casual contact of a TB case," if you intend to assess contact with a TB case in your investigation. Any epidemiologic comparisons (see Sect. 22.5.10) made to assess risk by contact would show that contact and only contact was the risk factor.

22.5.5 Find Cases Systematically and Record Information

Intensified case finding is the most important step of the initial investigation. It will provide the basis for all initial control measures as well as a list of persons to interview to determine risk factors for any epidemiologic study. The case finding using TST or IGRA should be applied to the entire group involved in the outbreak. TST should be read precisely and recorded to the nearest millimeter since in an outbreak different cutoff values than the standard may be used. During application of TST or IGRA, individuals should be questioned about persistent cough illness and other features of TB. All persons fitting a symptom-based definition for suspected TB disease should have sputum smear and culture. While administering the screening, key information needs to be collected on all individuals screened. This includes basic information about their place of work and living, age, sex, and occupation. One needs also to determine known risk factors for TB (e.g., immunodeficiency, diabetes, drug abuse) and BCG vaccination history. This information will be used later in the "descriptive epidemiology" step.

During this step of the investigation, identification of potential source cases of TB is critical. Since TB in a group of individuals invariably begins with a person who is actively expelling TB, knowing the individuals who were the origin of the outbreak will greatly assist in identifying subgroups and other groups at high risk. Additional related groups will also need case finding. For example, in a school out-

break, this could include family members of students, service personnel in a school, and individuals who recently graduated.

Case finding should also be extended to involve local clinics and laboratories. Investigators need to visit these potential sources and examine records for increases or other changes in frequency of tests for TB. In outbreaks in institutions with medical services such as prisons, universities, and medical facilities, a review of discharge diagnosis, sputum examination, and the radiology department can be very productive in identifying cases. If the capacity to perform drug sensitivity testing and genotyping is available, isolates should be characterized using these methods.

22.5.6 Assess Application of Standard Control Measures

Frequently, TB outbreaks arise from failure to apply routine TB control measures. As an extension of the case finding, all cases need to be assessed to see if they represent specific failures. During the case finding, one will identify new suspect cases of TB. A review of their illness and their attempts to seek treatment is necessary to understand and remedy the situation.

In addition to high sensitivity of case finding, prompt diagnosis and initiation of anti-TB therapy are the key goals of TB control. Each case of active TB in an outbreak should be evaluated for delays between onset of symptoms and diagnosis and between diagnosis and initiation of therapy. The appropriateness of the drug regimen should also be checked. The monitoring of drug resistance in the operational area where the outbreak occurred should be reviewed. The drug resistance pattern among the outbreak-associated cases is also necessary to guide therapy and to use as a marker for helping to determine linkage patterns between outbreak-associated cases.

The TB control program may also systematically screen high-risk groups. These could include prison inmates, persons in long-term care institutions, healthcare workers, and patients with HIV AIDS or other immunodeficiency. If the outbreak involves these high risk individuals, the appropriateness and completeness of application of routine screening need to be reviewed.

Disincentives to a smoothly running control program should also be identified. These include inappropriate control measures such as prolonged hospital isolation; exclusion of persons under appropriate drug therapy and/or with latent infection from work, school, or social activities; unintentional identification of TB patients to the community; requiring payment for TST, IGRA, sputum smears, or cultures; and other actions which reduce compliance with the TB control program.

22.5.7 Implement Standard Control and Prevention Measures

In outbreak investigations of other diseases, implementation of control measures is usually a step taken after more definitive information on exposures and risk factors is obtained. TB differs in that each and every case, whether active or latent, is an

opportunity for control. Persons with active pulmonary TB represent an immediate source of new infections. Effective control requires that they should be isolated for a few days while appropriate chemotherapy is initiated. Thereafter, they should be maintained on these appropriate drugs according to protocols. A high proportion of persons with latent TB found during outbreak will have recently acquired infection. Accordingly, they have a higher risk than the background population of developing new pulmonary TB over the subsequent 2 years. During outbreak, they should be treated prophylactically with an appropriate drug. One should reserve implementing other control measures until sufficient evidence in their support is gathered and assessed during the investigation.

22.5.8 Perform Descriptive Epidemiology

Accumulated data on cases and the background population involved in the outbreak should be characterized by time, place, and person. Incidence or attack rates of TB disease and prevalence rates of TB infection (TST or IGRA reactive) among different subgroups are compared. Those with the higher rates will be viewed as suspicious and hypotheses developed regarding the exposure.

22.5.8.1 Distribution in Time

Because TST and IGRA testing results are not linked to an onset of infection and because TB disease has a highly variable incubation period, the analysis of TB by time is often of minimal help—except to verify that a suspected source case preceded other cases. In institutional outbreaks, however, cumulative time of exposure should show increasing prevalence of latent TB as exemplified by an outbreak among hospital staff (Table 22.1; Alonso-Echanove et al. 2001). This is helpful to demonstrate that the problem as a whole was specific to the conditions in the institution as opposed to the background prevalence of TB in persons entering the institution.

22.5.8.2 Distribution by Place

Since TB is often transmitted in enclosed spaces, calculating rates by exposure to these areas is of high importance. These could include classrooms, indoor areas for special activities, school buses, break rooms, laboratories, and others. Areas with high rates of latent TB infection or TB disease suggest extended exposure to an individual with active pulmonary TB in that area. If active cases have been identified, then these areas may be combined according to the frequency that the person with the active case is in each specific area. If active cases have not been identified, then the search for active cases may be focused in these areas. As an

Table 22.1 Evaluation of potential risk factors (continuous variables) for *Mycobacterium tuberculosis* infection among healthcare workers from clinical and laboratory areas, Hospital Nacional Guillermo Almenara Irigoyen, Lima, Peru, March 1998 (Alonso-Echanove et al. 2001)

	Clinical areas[a]			Laboratory areas		
Variable	TST−	TST+	*P*	TST−	TST+	*P*
Duration of employment in years, median	8.8	11.7	<0.001	4	10.5	<0.001
Age in years, median	36	39	0.003	29.5	34.5	0.003

Note: Variables were compared using Student's *t* test or the Kruskal–Wallis test. *P* values are two-tailed and $P < 0.05$ was considered significant. *TST* tuberculin skin test
[a]Clinical areas include medical wards, the emergency department, and the intensive care unit

Table 22.2 Rates of active pulmonary TB among healthcare workers by work area, Hospital Nacional Guillermo Almenara Irigoyen, Lima, Peru, 1997 (Alonso-Echanove et al. 2001)

Hospital work area	HCWs	HCWs with active pulmonary TB	Attack rate[a]	RR (95 % CI)	*P*
Laboratory	172	12	6977	28.4 (6.4–125.4)	!0.001
Medicine wards	429	4	932	3.8 (0.7–20.6)	NS
Emergency department/ ICU	141	1	709	2.9 (0.3–31.5)	NS
Surgery wards	812	2	246	Reference value	–
Rest of hospital	844	0	0	Undefined	–
Total	2398	19	792	–	–

Note: Variables were compared using the ×2 test or Fisher's exact test. *P* values were two-tailed and $P < 0.05$ was considered significant. ICU, intensive care unit; HCW, Healthcare Workers
[a]Per 100,000 HCWs

example, in an outbreak among hospital staff, high rates of pulmonary TB among laboratory staff indicated transmission among that group (Table 22.2; Alonso-Echanove et al. 2001).

22.5.8.3 Distribution by Person

Rates by personal characteristics of TST prevalence and in larger groups of active TB are also very helpful. Age-specific rates should always be calculated and compared to the expected distribution of the high rates (e.g., very young, adolescents, and the elderly). Rates by occupation within institution or in the general community will also help focus on a specific hypothesis about exposure. If TST testing (in the previous steps) has been effectively applied to the involved group, then population factors will be known such as occupation, underlying risk factors, age, sex, and BCG vaccination. Underlying risk factors for active TB, such as smoking, substance

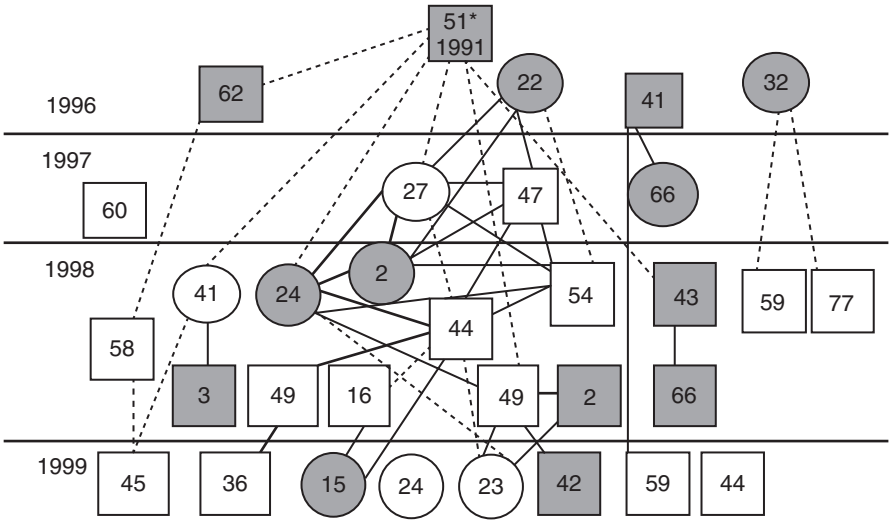

Fig. 22.1 Epidemiologic links for 31 patients according to age and sex (Fitzpatrick et al. 2001). *Possible source case; *circles* females; *squares* males; *unshaded symbols* fingerprint matches outbreak strain; *shaded symbols* epidemiologic link only; *solid line* link determined by means of traditional contact tracing methods; *dashed line* link established through social network investigation. Numbers within geometric shapes indicate age in years

abuse, diabetes, immunosuppression (including from HIV/AIDS), can be helpful in larger populations with sufficient numbers of active TB cases to make statistical comparisons. BCG will create only temporary TST reactivity and will not affect IGRA. BCG vaccination in the past should not be used to explain reactive TST during an outbreak. However, in outbreaks, persons with prior BCG tend to have larger areas of TST reactivity, and this should be noted and if necessary corrected for (through stratification by BCG) in the analysis. Information on known risk factors and BCG should be collected when one screens for latent infection in the case finding step of the investigation. Contact diagrams showing linkages between persons with infection or disease can be constructed to show presumed pathways of infection (Fig. 22.1; Fitzpatrick et al. 2001).

At this point in the investigation, the descriptive epidemiology and other established facts will often provide a clear understanding of the factors leading to the outbreak and identify risk factors for TB infection and disease as well as other correctable problems with TB prevention control and surveillance. Armed with this information, the investigators can develop a sound plan for control and follow-up of the outbreak. They may skip to the last three steps of the investigation (see Sects. 22.5.13–22.5.15): implementation of appropriate control measures and correcting defects in the TB control program, following the effect of control through the surveillance system, and communication of findings. However, in some TB outbreak

investigations, additional analytic, laboratory, and environmental studies are needed to answer important questions. In these situations, one needs to continue with the next step: develop a hypothesis.

22.5.9 Develop a Hypothesis

Hypothesis formation is based on known facts about TB, the descriptive epidemiology, plus all other factual information accumulated since the beginning of the investigation. This information is then digested into a testable proposition or hypothesis.

22.5.10 Evaluate Hypotheses Epidemiologically

In the analytic epidemiologic study, exposures, risk factors, and other key characteristics of the TB cases are compared to a comparison group which represents the population from which the cases arose. The two basic study designs used in outbreak investigations are the case–control study and the retrospective cohort study. In the case control study, the comparison group is a representative sample of the TB-free individuals. In the retrospective cohort, the entire population under investigation is used, and infection or disease rates are calculated and compared for each exposure of interest.

This approach is similar to the comparison of rates in the descriptive epidemiology described above (see Sect. 22.5.8) but differs in one main respect. In the analytic study, one obtains additional, more detailed exposure information that was not available during the descriptive epidemiology phase. This information addresses directly and in detail the exposures and risk factors stated in the hypothesis. This information may be obtained through questionnaire, direct observation, and/or specific measurements on the individuals. Using the hospital outbreak example from the descriptive epidemiology, a small, crowded, and unventilated common break room used by laboratory staff was identified as the main point of exposure in a retrospective cohort approach (Table 22.3; Alonso-Echanove et al. 2001).

22.5.11 Reconsider, Refine, and Reevaluate Hypotheses

This step is very rarely necessary in TB outbreaks. If the initial analytic study does not yield an answer to the hypothesis, the data collected needs to be reassessed, a new or modified hypothesis developed, and a new analytic study designed.

Table 22.3 Multivariate analysis of risk factors for *M. tuberculosis* infection among healthcare workers from clinical and laboratory areas, Hospital Nacional Guillermo Almenara Irigoyen, Lima, Peru, March 1998 (Alonso-Echanove et al. 2001)

	Clinical areas		Laboratory areas	
Variable	OR (95 % CI)	*P*	OR (95 % CI)	*P*
Contact with person with active TB	9.62 (4.25–23.52)	<0.001	–	NS
Helped collect sputum	3.13 (1.42–7.30)	0.004	–	NS
Duration of employment[a]	1.0013 (1.002–1.025)	0.02	–	NS
Use of common staff areas	–	NS	16.44 (4.9–64.4)	<0.001

Note: Analysis of infection controls for BCG vaccination and sex. $P < 0.05$ was considered significant

[a]Unit of change, 3 months

22.5.12 Compare and Reconcile with Laboratory and Environmental Studies

Several types of laboratory and environmental studies can support TB outbreak investigations. Environmental studies can demonstrate airflow patterns in hospitals, other institutions, aircraft, or other enclosed spaces, etc. Settling plates or air filters placed in high-risk areas, identified through epidemiologic investigation, can confirm whether *M. tuberculosis* is present in the air and, if so, in what concentration.

22.5.13 Implement Control and Prevention Measures

The primary goal of the investigation has been to control additional transmission of TB from the outbreak setting. By this time in the investigation, all standard control measures should already be implemented. These may require administrative procedures that facilitate diagnosis and treatment seeking among the involved group. The findings of the investigation will also support additional and special control measures. These will vary greatly from outbreak to outbreak. For example, in a hospital-based outbreak, control could involve engineering to redirect or filter air from laboratories and hospital isolation rooms. In outbreaks due to multiple drug-resistant TB, additional funding for improved laboratory capacity might be needed. In addition to the epidemiologic findings derived from the outbreak investigation, the design of control measures must take into account local limitations and other special local characteristics.

22.5.14 Initiate or Maintain Surveillance

In most situations, TB will already be under surveillance. During the investigation, one will have generated information about the effectiveness of the surveillance system. If deficiencies are found, these need to be corrected. In any case, one needs to pay close attention to continuing TB surveillance from the group or area represented by the outbreak. If TB reporting from the group does not show a decrease to acceptable levels, a follow-on investigation will be necessary. One should also consider more intensive monitoring of the treatment program in the involved group. TST or IGRA testing on individuals whose tests were negative during the investigation should be repeated 6–10 weeks after the identification and initiation of treatment of the last pulmonary TB case.

22.5.15 Communicate Findings

Communication of findings to local public health authorities and other organizations with a stake in the outcome of the investigation, as well as the groups of individuals affected directly by TB, is a necessary task throughout the investigation. From the beginning, investigators need to set up and maintain lines of communication.

As a final step to the investigation, one should brief all directly concerned with the outbreak. Different briefings for different groups who may have different information needs may be needed. A formal written scientific report is essential. It will serve as clear and precise communication of the recommendations and the principal findings which lead to the resulting recommendations. Others who may encounter similar TB outbreaks in the future may use it as a guide upon which they can build their own investigations.

TB outbreaks often arise from significant social issues. These can create difficulties both in applying control measures and in further investigation. These may be best remedied proactively by providing the entire group with clear information about TB disease, the risks of developing disease among exposed and among infected individuals, the comparative risks of prophylaxis and treatment, and the breadth of health consequences from TB disease. The information can be disseminated as a clearly written fact sheet. This should precede or be current with a presentation to a group in a situation where individuals are encouraged to ask questions. The speaker should have full command of TB disease and epidemiology and can put all essential facts in understandable terms of the general public. The speaker should be aware of local conditions, anticipate local social concerns, and adapt the presentations and/or information accordingly.

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Chapter 23
Preventive Therapy Against Tuberculosis

Lin Zhou and Eryong Liu

One-third of the world's population is currently infected with the tuberculosis (TB) bacillus (Manabe and Bishai 2000). The majority of infected individuals do not develop active TB but instead maintain the infection in a latent state. When the body's resistance is reduced, the TB bacillus may multiply, which can lead to active disease (Tu 2005). Many studies indicate that in the absence of anti-TB treatment, only 1–2 % of those infected will develop active disease soon after the infection. Approximately, 5–10 % of people who are infected with TB bacilli (but who are not infected with HIV) will become sick and/or infectious at some time during their life. When people with TB infection are coinfected with HIV, however, their probability of developing active TB increases to about 7–10 % per year (Riley 1993).

Studies have shown that using anti-TB drugs in people with latent TB infection (LTBI) can prevent active TB and consequently reduce the spread of TB in the population (Ziv et al. 2001). At present, this method has become an important measure in countries and regions that have a low prevalence of TB and better control of infectious TB patients (Tu 2005).

23.1 Efficacy of Preventive Therapy

Since its introduction in 1952, isoniazid (INH) has been widely used to treat active TB and also as a drug for preventing TB disease in those with latent infection.

Between 1950 and 1970, many trials were conducted in animals and humans in order to prove the effectiveness of INH in TB prevention. (Ferebee and Mount 1962; Mount and Ferebee 1962; Ferebee et al. 1963; Monaco 1964; Egsmose et al. 1965;

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Horwitz et al. 1966; Comstock et al. 1967; Holscher 1968; Ferebee 1970). The researchers asked three questions: (1) Could preventive therapy prevent TB infection? (2) Could preventive therapy eliminate existing TB bacillus in the body? (3) Could preventive therapy prevent active TB?

Studies have shown that the effect of INH in preventing TB infection and elimination of TB bacillus in the body is not obvious. For example, Ferebee and Mount (1962) and Ferebee et al. (1963) conducted a controlled trial of a 1-year treatment with INH given to each of four groups: students with negative tuberculin skin test, contacts of new patients, contacts of retreatment TB patients, and the mentally ill. The results showed that in terms of positive conversion rate of tuberculin skin test, there was no significant difference between the experimental groups and their control groups. In another trial conducted by Mount and Ferebee (1962), household contacts of TB patients who also had a positive tuberculin skin test were either controls or given a 1-year treatment with INH. This research found that the negative conversion rate of the tuberculin skin test was 6.3 % in the experimental group and 6.5 % in control group. This result indicates that INH therapy is not effective in the elimination of TB infection.

The usefulness of INH therapy in TB disease prevention, however, has been demonstrated. A number of randomized controlled trials of INH preventive therapy in different populations had been conducted in the USA, France, Denmark, and other countries (see Table 23.1) and had summarized the effect in over 900,000 person years. The results showed that INH preventive therapy could reduce 60 % of TB incidence. With full treatment compliance, the effect could reach 90 % (Getahun et al. 2010).

In the 1990s, with the rise of the AIDS epidemic, TB preventive therapy among people living with HIV/AIDS received great attention. In HIV-positive patients, the risk of progressing from TB infection to active disease is 20–37 times higher than in the HIV-negative. TB disease is associated with the deaths of more than 25 % of HIV positive patients. Thus, many studies explored the efficacy of INH preventive therapy in preventing TB disease among HIV-infected patients (Table 23.2).

In 1998, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) developed TB prevention strategies for the HIV-infected. In 2010, they also published "Guidelines for intensified tuberculosis case-finding and INH preventive therapy for people living with HIV in resource-constrained settings," which strongly recommended at least 6 months of INH preventive therapy for all HIV-infected persons (children and adults, including pregnant women) after the exclusion of the patients with active TB (WHO 2011).

23.2 Implementation of TB Preventive Therapy

Who will benefit from the TB preventive therapy, how should we select the regimen and what is the challenge faced by the preventive therapy?

Table 23.1 Randomized, controlled INH preventive therapy studies from 1962 to 1992

Reference	Location	Population (sample size)	Regimen	Follow up	Result
Ferebee and Mount (1962)	USA	Household contacts of TB patients (13,902)	12INH	10 years	Incidence (irrespective of TST): 6.2 ‰; TST positive: 11.1 ‰. The incidence was 1.4 ‰ from the first year to the seventh year. No new cases appeared in the tenth year.
		Household contacts of TB patients (13,945)	None		Incidence (irrespective of TST): 15.4 ‰; TST positive: 26.9 ‰. The incidence of the first year was 6.2 ‰. Incidence decreased annually and dropped to 0.5 ‰ in the tenth year.
Ferebee et al. (1963)	USA	Patients with mental disorders	12INH	10 years	Incidence: 6.2 ‰ with a 62 % reduction overall and a 68 % reduction for the population with a TST result of ≥10 mm.
		Patients with mental disorders	Control		Incidence: 0.72 %
Monaco (1964)	–	Patients with silicosis (811)	3INH/3NT for 2 years	5 years	Incidence: 7.3 ‰
					IPT didn't promote the fibrotic process of the patients with silicosis.
		Patients with silicosis (411)	Control		Incidence: 101.2 ‰
Horwitz et al. (1966)	Greenland	Villagers (4714)	$3INH_2/3NT/3INH_2$	6 years	Incidence: 5.7 %
		Villagers (3907)	Control		Incidence: 8.3 %
Comstock et al. (1967)	Alaska, USA	Eskimos	6INH	6 years	Incidence: 1.9 %
			Control		Incidence: 4.67 %
Holscher (1968)	Netherlands	Newly infected soldiers (133)	12INH	7 years	Incidence: 0.8 %.
		Newly infected soldiers (128)	Control		Incidence: 9.4 %,
International Union Against Tuberculosis Committee on Prophylaxis (1982)	Eastern Europe	Patients with fibrotic pulmonary lesions (28,000 randomly divided into four arms)	INH (12 weeks)	5 years	Incidence: 1.0 %
			INH (24 weeks)		Incidence: 0.49 %
			12INH		Incidence: 0.35 %
			Control		Incidence: 1.4 %
Hong Kong Chest Service et al. (1992)	Hong Kong, China	Patients with silicosis	3RFP	5 years	Incidence: 10 %
			3RFP + INH		Incidence: 16 %
			6INH		Incidence: 14 %
			Control		Incidence: 27 %

NT no treatment, *INH* Isoniazid, *IPT* Isoniazid Preventive Therapy, *RFP* Rifampin, *TST* Tuberculin skin test

Table 23.2 INH preventive therapy studies in HIV-positive populations

Reference	Location	Population	Regimen (sample size)	Follow up	Result
Pape et al. (1993)	Haiti	HIV+ people randomized into 2 arms (118)	12[INH + B6] (58)	33 months	Significant difference in incidence between the preventive therapy arm (2.2/100 person-years) and the control arm (7.5/100 person-years, RR = 3.4, 95 % CI 1.1–10.6);
			12[B6 only] (60)		In those with a positive TST, there was a significant difference in incidence between the preventive therapy arm and control arm (RR = 0.33, 95 % CI 0.14–0.77).
					Preventive therapy in the HIV positive/TST positive could significantly reduce the incidence and mortality.
Whalen et al. (1997)	Kampala, Uganda	HIV+ people randomized into 4 arms (2736)	6INH (536)	15 months	Incidence of the preventive therapy arms was lower than that of the control arm (P = 0.002). Compared with the control arm, RRs for TB were 0.33 (95 % CI 0.14–0.77), 0.40 (95 % CI 0.18–0.86), and 0.51 (95 % CI 0.24–1.08), respectively.
			3[INH + RFP] (556)		
			3[INH + RFP + PZA] (462)		
			Control (464)		
Mwinga et al. (1998)	Lusaka, Zambia	HIV+ people randomized into 3 arms (1053)	$6INH_2$	1.8 years	Incidence was lower in therapeutic arms (rate ratio = 0.60, 95 % CI: 0.36–1.01, $P = 0.057$). For those with TST result of ≥5 mm, significant difference in incidence between the preventive therapy arms and control arm. (2.5 vs. 9.2/100 person year, RR = 0.27 95 % CI 0.08–0.87).
			$3[RFP + PZA]_2$		The protective effect of INH was 74 %.
			Control		No significant difference in mortality between all arms. Protective effect of therapy declined after treatment; by 18 months, rates of TB were similar across all arms.
Akolo et al. (2010) systematic review	Multiple countries	Twelve randomized controlled trials HIV+, TST+/−, without active TB (8578)	(Varied)	(Varied)	The incidence of the preventive therapy arms was significantly lower than the control arm (RR = 0.68, 95 % CI 0.54–0.85). Preventative therapy was more effective for those with a positive TST (RR = 0.38, 95 % CI 0.25–0.57).

23.2.1 Who Should Be Given TB Preventive Therapy?

A point that needs to be emphasized is that patients with active tuberculosis should be excluded from prophylactic treatment. Treating active TB with preventive therapy is ineffective and can lead to the generation of drug-resistant TB. Preventive therapy is drug medication for persons with latent TB infection. Therefore, the first step in preventative therapy is to identify patients with LTBI. Currently, the diagnosis of TB infection includes the following two methods: tuberculin skin test and interferon-gamma release assay (IGRA).

23.2.1.1 Tuberculin Skin Test (TST)

Tuberculin, also known as tuberculin purified protein derivative (PPD), is a standardized killed extract of *Mycobacterium tuberculosis* bacillus. The tuberculin test originated in the late nineteenth century. It is still the most widely used method in the diagnosis of LTBI.

The WHO's recommended method for administering the TST is to inject 0.1 ml of tuberculin PPD into the inner surface of the lower 1/3 forearm. The reaction should be read between 48 and 72 h after injection and the induration measured in millimeters not including erythema (redness).

Currently the USA, the UK, Australia, and other countries have definitions for positive TST results (Cohn et al. 2000; Konstantinos 2010) which are summarized as follows:

- Induration diameter of ≥ 5 mm is considered positive in the following groups:
  - HIV-infected people
  - Recent contacts with infectious TB
  - Organ transplant recipients or people using immunosuppressive drugs.
- Induration diameter of ≥ 10 mm is considered positive in the following groups:
  - Immigrants from high TB prevalence countries within the last 5 years
  - Intravenous drug users
  - People living in congested areas (such as prisons, nursing homes, hospitals, shelters, etc.)
  - TB laboratory staff
  - People with other diseases which result in an increased risk of TB such as diabetes, long-term use of corticosteroids, leukemia, end-stage renal disease (kidney failure), chronic malabsorption syndrome, low body weight, etc.
  - Children under 4 years old or TB high-risk infants and adolescents exposed to TB adults.
- Induration diameter of ≥ 15 mm is considered positive in the following groups:
  - General population with no known risk of suffering from TB

23.2.1.2 Interferon Gamma Release Assay (IGRA)

The recently developed IGRA is an in vitro blood test to detect interferon gamma (IFNg) produced by immune cells after stimulation by *M. tuberculosis* infection.

IGRAs can differentiate between natural infection with TB and BCG vaccination. The assay has a significantly higher specificity than the TST and improved sensitivity in HIV-positive patients. Currently, this assay is widely used. The three commercial test kits are the T-SPOT.TB kit (UK, Oxford Immunotec Limited), the QuantiFERON-TB GOLD (QFT-G) kit, and the QuantiFERON-TB GOLD In-Tube (QFT-GIT) kit (Australia, Cellestis Limited). These tests have FDA approval in the USA, CE Mark approval in Europe, and MHLW approval in Japan.

In theory, TB prophylactic treatment should be provided to all diagnosed with LTBI. However, TB prevalence is different around the world, and not all people infected with TB will develop disease. Due to limited resources and other factors, it is unnecessary and impractical to blindly provide preventive therapy to all people with LTBI.

In countries or regions implementing TB preventive therapy, all regard the high-risk TB groups as a priority. However, the therapy is slightly different between different countries. For example, in the USA, if a person has recent contact with an infectious TB patient and is aged ≤5 years or is immunocompromised, TB preventive therapy is recommended even if the contact's TST or IGRA result is negative (Centers for Disease Control and Prevention (CDC) 2010). Similarly, the WHO recommends preventative treatment for those infected with HIV and for children younger than 5 years who have close household contact with smear-positive TB patients (WHO 2011).

23.2.2 Selection of Preventive Regimen

The selection of preventive regimen is based on the feasibility, adverse response of the regimen, and compliance issues.

23.2.2.1 INH Regimen

INH is the first choice of TB preventive therapy since its advent. INH given daily or twice a week for 6–12 months is the most commonly used treatment option (American Thoracic Society 1986). The findings in Eastern Europe indicate that a 6-month INH treatment is effective but 12-month INH treatment is better. However, the completion rate of 12-month INH was significantly reduced, thereby reducing the therapeutic effect (Monoco 1964). A cost-benefit analysis study for this research conducted by Snider et al. (1986) indicated that 6-month INH is more cost-effective than 12-month INH.

In 2000, the American Thoracic Society recommended a 9-month course of INH treatment. This was based on the recommendation of Comstock (1999) who determined that a 6-month treatment is insufficient, a 12-month regimen had a low completion rate, and a 9-month treatment is the best option with effectiveness up to 90 %. However, other research indicates that the completion rate of a 9-month INH preventive therapy is also low, less than 50 % (Jasmer et al. 2000; LoBue and Moser 2003).

The main challenges of INH preventive therapy are that the drug has been used in TB treatment for decades (leading to higher resistance rates) and that it requires a long course of treatment (leading to lower compliance and difficult medication management).

23.2.2.2 Rifampicin (RIF) Regimen

The advent of RIF shortened chemotherapy for active TB cases to 6 months. The experts also began to study the feasibility of RIF in reducing the duration of preventive therapy.

A study for RIF application in preventive therapy from Hong Kong showed that a 3-month treatment with RIF and a 3-month treatment with RIF in combination with a 6-month treatment of INH has the same effect in TB prevention: both significantly lower the rate of developing TB compared to the control group. A 3-month treatment with RIF is most easily accepted, has the highest completion rate, and has no liver toxicity (Hong Kong Chest Service et al. 1992). Since then, many studies have proven that a 4-month treatment with RIF alone was as effective as a 6–9 month treatment of INH, but with a significantly higher treatment completion rate and a very low incidence of severe adverse reactions (especially liver toxicity) (Page et al. 2006; Lardizabal et al. 2006; Menzies et al. 2004; Ziakas and Mylonakis 2009).

In 2000, the American Thoracic Society recommended a RIF regimen as an alternative for preventive therapy (Akolo et al. 2010). The Canadian Thoracic Society subsequently also recommended this regimen (Long and Ellis 2007).

23.2.2.3 Rifampicin (RIF) and Pyrazinamide (PZA) Regimen

RIF and PZA are both potent bactericidal drugs. PZA can kill the slow-growing *M. tuberculosis* in cells, thereby providing a theoretical basis for prevention of TB and TB relapse.

The fact that a RIF + PZA regimen has an equal efficacy with INH regimen was first proved in animal experiments (Lecoeur et al. 1989). Many studies have shown the regimen's effectiveness in HIV-infected people (Gao et al. 2006). A multicenter randomized controlled study (with subjects from the USA, Mexico, Haiti, and Brazil) showed that a 2 month treatment of RIF + PZA was comparable, in terms of safety and efficacy, to 12 months of INH, but with a higher completion rate (Gordin et al. 2000).

In 2000, the American Thoracic Society recommended this regimen in patients infected with HIV and as an alternative treatment for the HIV negative (Cohn et al. 2000). A meta-analysis showed that in terms of the efficacy, this regimen is comparable with INH in patients with and without HIV infection. However, this regimen was later found to induce serious adverse reactions including liver toxicity and death (Gordin et al. 2000; CDC 2001; Gao et al. 2006). Subsequently, the American Thoracic Society stressed in its guideline that this regimen must be used under strict monitoring (American Thoracic Society et al. 2003).

23.2.2.4 Regimen of Isoniazid (INH) with Rifampicin (RIF) or Isoniazid (INH) with Rifapentine (RFT)

A meta-analysis showed that in terms of efficacy and the incidence of adverse reactions, a 6-month INH + RIF regimen is comparable with 6- or 9-months of INH (Ena and Valls 2005). A Canadian observational study showed that the completion rate of a 6-month INH + RIF regimen twice a week is significantly higher than a daily INH regimen (McNab et al. 2000).

RFT is a long-acting rifamycin derivative, with five times the half-life of RIF, and is more suitable for short duration intermittent preventive treatment. A study in China showed that the compliance of RFT for high-risk groups was 83.9 %, and the incidence of adverse drug reactions was 7.2 % (Gao et al. 2004). For INH, these two rates were 72.5 % and 10.2 % respectively. The 2-year cumulative incidence of active TB in a RFT-containing regimen was 2.67 % and the and 5-year cumulative rate was 6.44 %, which was comparable with INH group and significantly lower than the control group (which did not receive preventive treatment). One small trial found that the incidence of 3–4 grade liver toxicity in a 3-month INH + RFT was significantly less than 3 months of INH + RIF group (1 % vs. 10 %, p <0.001), with no difference in the incidence of TB (Schechter et al. 2006).

23.3 The Challenges of Preventive Therapy

The main challenges of preventive therapy are adverse drug responses and patient compliance.

23.3.1 Adverse Drug Response

INH for a 6–9 month period is the most widely used treatment regimen in TB preventive therapy. The most common adverse event is liver toxicity. The first event raising concern about liver toxicity caused by INH preventive therapy happened in USA in 1970. Liver toxicity occurred in 19 people out of 2321 close contacts receiving INH

preventive therapy, with 2 deaths (LoBue and Menzies 2010). Following this, the US Public Health Service conducted an in-depth investigation including 14,000 patients from 21 health care agencies (Garibaldi et al. 1972). Among these, 174 (1.3 %) experienced liver toxicity and 8 patients died. The risk factors were patient age greater than 35 years and alcohol abuse. The American Thoracic Society hence changed the indications for INH preventive therapy to exclude patients over 35. A meta-analysis including six studies with 38,000 people showed that the overall incidence of liver toxicity is 0.6 % (Garibaldi et al. 1972). Through strictly limiting the subjects and close monitoring, INH-induced mortality has been greatly reduced in the past 30 years (Kopanoff et al. 1978; Steele et al. 1991).

Adverse reactions to INH preventive therapy also include peripheral neuropathy, which is caused by inhibition of the metabolism of pyridoxine. Peripheral neuropathy is rare in healthy people. It is more common in chronic alcoholics, the malnourished, and pregnant women (Goldman and Braman 1972; Snider and Caras 1992; Salpeter 1993).

In order to ensure the safety and effectiveness of INH preventive therapy, the US *Latent Tuberculosis Infection: A Guide for Primary Health Care Providers* provides concrete steps in patients' monitoring and education in the course of treatment (American Thoracic Society et al. 2003):

- Patient education
- Health care professionals should explain to the patient the process of the disease and the rationale for medication in the absence of symptoms or radiographic abnormalities. Stress the importance of completing treatment for LTBI, and discuss the possible side effects of LTBI medications in the course of treatment. Discuss how to deal with adverse reactions and the need to report them to the doctor.
- Clinical monitoring
- The patient should visit the health care provider on a monthly basis to be checked for signs of hepatitis and evaluation of the patient's compliance, possible adverse reactions, and drug interactions. If patients taking INH or RIF experience possible adverse reactions, they are advised to stop medication and consult a doctor as soon as possible.
- Laboratory testing
- Routine baseline laboratory monitoring results are not necessary. Laboratory testing at the start of LTBI therapy is recommended for patients with any of the following factors: liver disorders, history of liver disease, regular use of alcohol, risks for chronic liver disease, HIV infection, pregnancy or in the immediate postpartum period. After baseline testing, routine periodic testing is recommended for persons who are at risk for hepatic disease and others who had abnormal initial results. Laboratory testing for patients who have symptoms suggestive of hepatitis or who have jaundice is mandatory. Patients should be instructed at the start of treatment, and at each monthly visit, that if symptoms of hepatitis develop, they should to stop treatment and seek medical attention immediately.

If the patient is free of hepatitis symptoms, blood levels of aspartate transaminase (AST) and alanine transaminase (ALT) can be elevated up to five times the upper limit of normal and still be acceptable.

Studies have shown clinical monitoring of patients can significantly improve treatment completion rates.

23.3.2 Compliance Issues

Another problem for TB preventive therapy is low patient compliance. TB preventive therapy should be carried out in patients under voluntary conditions, as many patients do not accept preventive therapy when it is recommended. In a retrospective study, among 720 patients meeting the conditions of prophylactic treatment, 123 (17.1 %) declined the treatment. According to reports, adherence to INH therapy ranged from 30 to 70 % (American Thoracic Society et al. 2003). U.S. data show that only 60 % of patients who began INH preventive therapy completed at least 6 months of treatment (Girling 1982). Patient compliance is influenced by factors such as the length and complexity of the treatment regimen and adverse reactions. A study in Haiti and other countries showed that a 2 month combination treatment of RIF + PZA had significantly higher compliance (80 %) than a 6 month INH regimen (55 %) (Horsburgh et al. 2010).

Multi-country studies have shown that the treatment completion rate for a 2 month RIF + PZA combination regimen reached 80 % while that of a 12 month INH regimen was 69 % (Camins et al. 1996).

In the USA, it is estimated that about 30,000–400,000 people will start preventive TB treatment, with 90 % of them taking INH (Horsburgh and Rubin 2011). INH-induced adverse reactions result in decreased patient compliance and low treatment completion rate. The US *Latent Tuberculosis Infection: A Guide for Primary Health Care Providers* divided the factors affecting the patient compliance into three categories: medical-related factors, such as long waits and inconvenient access times; patient-related factors, such as patients residential instability, lack of financial resources, and poor access to health care; and treatment-related factors, such as adverse reactions and the complexity and duration of treatment (CDC 2010). The guideline also put forward measures to improve patient compliance:

- Collaborate with local health department to provide patients with DOT, case management to coordinate care and services, free or low-cost medication, economic incentives, etc.
- Provide education and instructions for patients
- Reinforce patient education in each visit
- Ensure confidentiality
- Suggest or provide reminders to patients

In many studies, directly observed preventive therapy (DOPT) has been proved effective in improving patient compliance. In a DOPT project conducted in San

Francisco in 1996, the treatment completion rate was 70.3 % in the DOPT group, compared with only 47.9 % in the self-administered medicine group (p <0.001) (White et al. 2003).

23.4 The Implementation Status of Preventive Therapy and Recommendations

In the past 30–40 years, TB preventive therapy has become an important TB control strategy in many high-income countries (e.g., USA, Canada, and Australia). Early in 1965, the USA began INH preventive therapy for people with LTBI (Gordin et al. 2000). In these countries, the first priority in TB control is the early diagnosis and treatment of active TB patients to reduce the spread of infection in the population. The second step is to diagnose and treat LTBI (Sterling et al. 2006).

Although the main burden of LTBI lies in the Southeast Asia, Western Pacific, Africa, and Eastern Mediterranean regions (White et al. 2003), the high cost, poor acceptability, and difficulties in treatment management (including monitoring and treatment of adverse reactions) limit the application of preventive therapy in these low-income countries. An analysis of many studies shows that preventive therapy has a very small public health benefit: less than 10 % of those with LTBI benefit from it (Runyon 1965; CDC 1996; Heal et al. 1998; Corbett et al. 2003). This is due to many factors. Patients may not be willing to accept the screening for latent infection, or they may accept the screening but not come back for a reading of the test results, therefore positive results go unreported. Patients may refuse preventive therapy or fail to adhere to the therapy. Doctors may not follow the prescription of national guidelines. These and other reasons have reduced the public health benefits of preventive therapy in these settings. The importance of TB preventive therapy in TB control programs depends on local economic conditions and TB prevalence. In low prevalence areas, TB preventive therapy plays an important role in TB control work; TB epidemics are averted by preventing LTBI from developing into active TB. In high TB epidemic areas, however, the primary focus is to control the source of infection and treat active TB, rather than treating LTBI to prevent the progression to active disease.

Although TB preventive therapy has been proven to be a very effective measure in preventing the incidence of TB, from an epidemiological perspective, the incidence of TB depends on the incidence of TB in high-risk groups. The proportion of these high-risk populations being offered effective preventive therapy and the percentage of them completing the therapy have an impact on TB epidemic control. However, for lower- and middle-income countries with limited resources, one must consider the public health benefits and feasibility of preventive therapy and recognize the many challenges, including the protection of personnel, funding support, identification and enrollment of persons for therapy, determination of treatment regimen, effective drug supply and management, patient monitoring, impact evaluation, etc. Every aspect must be carefully prepared and implemented.

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Chapter 24
Case Study: The Strategy and Implementation of Preventive Treatment for TB Infected College Students in Beijing

Xiaoxin He and Li Bo

24.1 Introduction

Currently, 1/3 of the six billion people in the world are infected with *Mycobacterium tuberculosis* (Manabe and Bishai 2000). Without treatment, about 5–10 % of infected people will develop active TB in their lifetime. The measures of TB prevention and control mainly include three aspects: controlling the source of infection by reducing the transmission through detection and treatment of infectious cases, giving BCG vaccination to newborns, and giving preventive treatment to people who have latent TB infections (LTBI) (Zhang et al. 1998).

The purpose of preventive treatment for those with LTBI is to kill *M. tuberculosis* via chemotherapy. This can lower the risk of developing active TB and its serious complications. This may also reduce the occurrence of active TB caused by the resurgence of the latent TB infection.

During the past 30–40 years, TB preventive treatment has become an important strategy in many high-income countries such as the USA, Canada, and Australia. Because of the high cost of preventive treatment, the follow-up during the course of treatment, and the monitoring of adverse reactions, the application of preventive treatment has been limited in low- and middle-income countries. Studies have shown that preventive treatment in low-risk groups is costly. Therefore, many countries only do this treatment in high-risk groups (Yan and Duanmu 2003).

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24.2 TB Control in Beijing

Beijing had a high prevalence of TB before the founding of The People's Republic of China (PRC) in 1949. After then, Beijing began to implement measures of TB control. Hospitalization was the main management tool for TB cases. Each year, about 15,000 cases were treated under this model. However, due to the long course of treatment required (18 months with isoniazide, para-aminosalicylic acid, and streptomycin) and lack of appropriate treatment management mechanisms, patient compliance was poor. Before 1978, approximately 60 % of the cases could not complete the treatment and the cure rate was less than 50 % (Beijing Research Institute for Tuberculosis Control 1979).

Because of treatment failure in the initial-treatment cases, the number of infectious cases had been numerous. According to the result of the 1979 national TB epidemiology sampling survey, 65.5 % of smear-positive TB cases detected in the survey were not cured (Ministry of Health 1981).

Therefore, starting in 1978, Beijing introduced and implemented Directly Observed Treatment, Short Course (DOTs) recommended by the WHO. The DOTs strategy was firstly implemented in the initial smear-positive pulmonary TB cases in rural areas, and then gradually expanded to urban districts. In 1986, DOTs strategy was extended to the retreatment of smear-positive pulmonary TB cases.

To prevent infection, the Bacillus Calmette–Guérin (BCG) vaccine was widely given to newborns in Beijing starting in 1952. The rate of neonatal BCG vaccination continued to increase every year. The rate was maintained at over 95 % since 1990. Starting in 1996, the effect of neonatal BCG vaccination was monitored. The rate of the neonatal BCG vaccination and the success rate of the vaccination (indicated by a positive tuberculin skin test (TST) 12 weeks after vaccination) were both more than 98 % after 1998 (Beijing Research Institute for Tuberculosis Control 2005).

In response to the natural decline of TB infection under the modern measures of TB control, neonatal BCG vaccination was halted in a pilot study in the of Shunyi district of Beijing starting in July of 1988. In 1995, purified protein derivative (PPD) and international standard test technology were used in the tuberculin skin test for pupils born between 1988 and 1989 in Shunyi district. The TB infection rate was reported at 1.4 %. The estimated annual infection rate was 0.19 %. This demonstrated that the modern measures of TB control had great impact on the rate of TB infection (Zhang et al. 1998).

The national TB epidemiology sampling survey showed that the smear-positive prevalence of TB in Beijing was 127/100,000 in 1979 (national prevalence: 187/100,000), 56/100,000 in 1985 (national prevalence: 156/100,000), and 16/100,000 in 1990 (national prevalence: 134/100,000). The average annual reduction rate was 17 %. Beijing has the lowest active pulmonary TB prevalence in China (Ministry of Health 1992).

24.3 TB Infection and Preventive Treatment in Beijing Schools and Students

As mentioned above, the epidemic of TB was significantly reduced in Beijing during the 1990s. However, the phenomenon of TB clustering incidence (more than three cases in a class or in several classes nearby) became a prominent concern for TB control in Beijing. The spread of TB in school campuses directly threatened the health of students and faculty, the stability of the campus, and the public health of the capital.

Beijing is the home of 3593 various kinds of schools and more than three million students, which accounted for 19.6 % of the resident population in 2012. There are 80 colleges with a total of over 500,000 students. Of these, 80 % came from provinces with relatively high prevalence of TB (Liu et al. 2002). They are apt to suffer from TB because of their decreased resistance due to their age (their endocrine systems are in transition), new surroundings, stress, and intense study. TB spreads easily in schools if new cases are not detected promptly. Reducing the incidence of TB on college campuses and enhancing the monitoring of new cases play an important role in the control of TB in Beijing.

24.3.1 A Pilot Study of Preventive Treatment Among College Freshmen with a Strong PPD Reaction

Monitoring freshmen by the PPD test and giving preventive treatment to those with strong PPD reactions could decrease active TB cases, thus reducing the incidence of TB in the whole campus. Preventive treatment is important for school wide TB control.

In 1996, a pilot study in Tsinghua and six other universities in Beijing provided preventive treatment to freshmen with strong PPD reactions. The preventive chemotherapy consisted of a 3-month course of rifapentine plus isoniazid twice per week for a total 25 combined doses. The dosages of rifapentine and isoniazid were 0.6 g each for people who weighed more than 50 kg. For people less than 50 kg, the dosage were 0.45 g of rifapentine and 0.5 g of isoniazid. Members of the Red Cross Society supervised the students following DOTs procedure and reported adverse events to the school hospital staff. Staff of the Haidian District TB Center sent medicines to the school hospital and provided supervision once every 2 weeks. They would monitor the administration of medicine, the adverse reactions, the incidence of TB, and also address the relevant issues. There were 19,885 freshmen monitored with PPD in the seven colleges. The students with a strong TST (PPD) reaction with an induration 15 mm or greater (with or without papules and blisters and whose chest X-rays were normal) were divided into two groups: the intervention group and

the control group. The intervention group was given health education and preventive treatment, which 90 % completed. The occurrence rate of adverse reactions was 3.3 %, the proportion of discontinuation due to adverse reaction was 1.0 %, and no serious adverse reactions occurred. The control group was given only health education (Liu et al. 2005).

After a 4-year follow-up, the average annual incidence rate was 64/100,000 in the intervention group and 255/100,000 in the control group. The protective rate for preventive treatment to reduce the incidence of TB was 74.8 %. The preventive chemotherapy was safe, effective, and feasible for the freshmen with strong PPD reactions (Liu et al. 2005). Another study suggested that the PPD reaction standard of preventive treatment for the freshmen should require an induration size greater than 15 mm or with papules or blisters (Tu et al. 2006).

24.3.2 Implementation of the Freshmen PPD Monitoring Project

Since 2004, the Beijing Health Bureau, the Beijing Municipal Education Commission, and the Beijing Finance Bureau have united to carry out free TB screening for all college freshmen in Beijing. This project includes the following:

- Provide free TST with PPD for all freshmen with free TB examination (e.g., chest X-ray) for those with symptoms of TB or with strong TST (PPD) reactions. This enables earlier detection, isolation, and treatment of TB cases.
- Give preventive treatment (with informed consent) to those with strong PPD reactions to reduce the TB incidence in the student group.
- Give health education on TB prevention and treatment to school leaders, school doctors, teachers, and the students, thus improving the level of TB control in schools.

Students with strong PPD reactions were informed of the TB incidence risk, health risk if they developed active TB, protection rate of the preventive treatment, and details of the preventive treatment (e.g., drugs, dosage and courses, possible adverse reactions). The students firstly signed the informed consent, and then they would be given the preventive treatment on the basis of normal liver function. During the treatment, any adverse reaction would be monitored by the school doctors, and the students would be advised to check their liver function at the end of the first month. In order to ensure the effect of the treatment, the preventive treatment was monitored by the class teacher and the class leader under the management of the school hospital. Technical support would be provided by the district TB center.

Of the 750,948 freshmen who were monitored by TST (PPD) in the universities in Beijing between 2004 and 2007, 105,123 students (14.0 %) had strong PPD reactions. Of these, 803 patients with active pulmonary TB were detected, and the prevalence was 107/100,000 (Table 24.1). All active cases were registered and given standard treatment. Strict management was given in order to ensure the completion

Table 24.1 The implementation of the free TST screening project between 2004–2007 in Beijing (He 2008)

Year	Total students tested	Students with reaction ≥ 15 mm	Rate (%)	Students with active TB	Rate (1/100,000)	Students receiving preventive treatment	Rate (%)
2004	137,162	23,197	16.9	191	139.3	3210	13.8
2005	201,285	28,659	14.2	209	103.8	2332	8.1
2006	208,344	27,508	13.2	204	97.9	2726	9.9
2007	204,157	25,759	12.6	199	97.5	2269	8.8
Total	750,948	105,123	14.0	803	106.9	10,537	10.0

of the treatment. Many infectious cases were detected and controlled by carrying out this project, thus blocking the spread of TB in campus (He 2008).

From the beginning of the project, about 10 % of the close contact students with strong TST (PPD) reaction accepted preventive treatment, despite the strong measures taken to assure the treatment. Although the protection rate among students who accepted preventive treatment was 75 %, due to the low acceptance rate of preventive treatment, the project's overall reduction of risk of developing TB in students with strong TST(PPD) reaction was about 7.5 %.

There are two main reasons freshmen with strong PPD reactions did not accept preventive treatment. First, the freshmen were healthy, without symptoms or discomfort from TB, and did not believe they would develop active TB. Students would carefully weigh the benefits obtained from the preventive treatment with the risk of adverse reactions. Second, since 2005, the number of freshmen has exceeded 200,000 per year. Approximately 25,000 students tested had a strong PPD reaction. This large number made it more difficult to supervise the freshmen undergoing preventive treatment than those in treatment for active TB. Additionally, the medical staff, particularly in the TB district center, had a negative perception of preventive treatment due to the risk of adverse reactions.

The effectiveness of preventive treatment was affected by the following factors:

- Risk for developing active TB: the size of the induration of the tuberculin skin test in children and adolescents is positively correlated with the risk of developing active TB (Tu et al. 2006).
- The degree of adherence to treatment: many students with strong TST (PPD) reaction do not adhere to the treatment due to the length of treatment and concerns about adverse reactions.
- The effectiveness of the preventive chemotherapy.

The targets of preventive treatment are those with LTBI, not clinical TB patients. It is necessary to exclude the active TB cases in students with strong TST (PPD) reaction, in order to avoid possible development of drug-resistant TB. Preventive treatment should be given with informed consent. During the course, any adverse effects should be monitored and treated promptly.

24.3.3 Preventive Treatment Amid TB Outbreaks in Colleges

Tuberculosis outbreak is defined here as three active TB cases with epidemiological linkage detected in a short period of time (3 months or 6 months). It is a result of the spread of TB infection in a close contact group. Because of the significantly higher incidence in a short time and within a small area, it is best to implement preventive treatment for the infected people to reduce the occurrence of new TB cases (Beijing Health Bureau 2009).

Since 2007, preventive treatment strategies have been actively carried out in close contacts with strong TST (PPD) reactions. Preventive treatment can significantly reduce secondary TB cases. In a TB outbreak in a college in 2009, 91 % of the close contact students with strong TST (PPD) reaction agreed to accept preventive treatment after health education. Excluding subjects with contraindications such as abnormal liver function, 30 % of the students with strong PPD reaction accepted preventive treatment. A 9-month follow-up study showed that the TB incidence in students who took preventive chemotherapy (1/66) was significantly lower than in those not accepting preventive treatment (8/126; He et al. 2015). Actively carrying out preventive treatment for the students who are in close contact with TB cases and have a strong PPD reaction has become one of the basic principles in The Beijing Health Bureau's published "Working standards of TB control in the schools of Beijing" (2009).

24.4 Prospects of Preventive Treatment in Beijing

Preventive treatment is for healthy people only infected with *M. tuberculosis*. The benefit of receiving preventive treatment must be higher than the risk of developing adverse reactions.

Not all people infected with TB will develop active infection. Because of the numerous infected people, giving preventive treatment to all people infected with TB would be unnecessary and unrealistic. High-risk subjects who need preventive treatment are as follows: infected children living in households with a smear-positive pulmonary TB case; children and adolescents with tuberculin skin test indurations more than 15 mm; people with inactive TB lesions without anti-TB treatment; TB-infected subjects coinfected with HIV; and other high-risk TB-infected subjects with diabetes, silicosis, immunosuppression, etc. As the region with the lowest TB prevalence in China, preventive treatment would be promoted in Beijing in the following respects:

First, to standardize preventive treatment, especially in the case of a TB outbreak. Publish guidelines for how to judge the degree of TB spread, implement health education and mobilization for preventive treatment, and supervise and guarantee compliance of preventive treatment.

Second, to improve preventive treatment for children infected with TB. Research indicates that children in close contact with infectious TB cases appear to have a greater risk for being infected with TB and developing active TB. Infants and children under 5 years who are TB infected have a higher risk of developing active TB than those over 5 years old and usually develop active TB within the first 2 years of infection. Therefore, it is particularly important to screen children who are in close contact with infectious cases and give preventive treatment to them (Yan and Duanmu 2003).

Third, preventive treatment should be supplied for persons coinfected with TB and HIV and the TB infected suffering from diabetes. Compared with patients infected with TB only, those with concomitant diabetes have a 4–8 times greater risk of developing active TB, and those coinfected with HIV/AIDS have 30 times the risk of developing active TB (Yan and Duanmu 2003). TB-infected patients with silicosis also have a higher risk of developing active TB. Of the silicosis patients with pulmonary TB, 20 % have stage I (localized) silicosis, 30 % are stage II (advanced), and over 50 % are at the most advanced stage (IV). People who have used immunosuppressive agents for a long time are also high-risk subjects for developing TB.

In 2006, the WHO published *Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children* to standardize the diagnosis and treatment of children with TB as well as to promote preventive treatment in infected children. To protect the physical and mental health of the children, this work has been implemented as part of Beijing's TB control program with plans to expand in the future.

Preventive treatment is a powerful tool to reduce the risk of progression to active TB in the TB infected, improve the quality of life in high-risk subjects infected with TB, and control the spread of TB in the population. The preventive treatment for the high-risk subjects will be actively carried out and gradually standardized in Beijing. This protocol will be dynamically supplemented and improved to increase the level of TB control in China's capital and one of the most populous cities in the world.

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Chapter 25
Case Study Pakistan: Society Awareness and Media Coverage for TB Prevention and Treatment

Muhammad Amir Khan and Aamna Khalid

25.1 Introduction

The importance of media in creating awareness, shaping perceptions, forming opinions, and influencing policy makers in favor of sound public health interventions has been internationally recognized. Media has always proved to be the most effective tool in promoting awareness among masses. It assists in providing the public with the information they need to make intelligent choices as citizens. Most donors spend a large amount of their funding for raising awareness through media. Some major examples are the HIV AIDS campaign funded by World Bank, tobacco control campaign of World Lung Foundation, and the tuberculosis (TB) control campaign of The Global Fund. However, adapting media campaign to the health services and sociocultural context is required for optimal results.

25.2 Pakistan Context

Pakistan belongs to the South Asian region and covers an area of about 796,095 km^2. Administratively, Pakistan comprises five provinces besides some federally controlled areas and the states of Azad Jammu and Kashmir. The current population of the country is estimated at about 182 million, with about 33 % of the population under 15 years of age (World Bank 2015). The annual population growth is 2.1 %, with 166.3 persons per square kilometer (range: 18.9–358.5). About 23 % of the

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population is living below the international poverty line of US$1.25 per day in overcrowded places with poor hygiene (Ministry of Finance 2010). In 2009, the life expectancy at birth was 67 years, with a crude death rate of 7 % (National TB Control Program (NTP) 2006). The overall adult literacy rate was 57 % (men: 69 %, women: 45 %) with an unemployment rate of 5.5 % (NTP 2008). The geographic distribution of the population is uneven. Pakistan has primarily an agrarian economy with almost 67.5 % of its population living in rural areas (NTP 2008). As per a report from the United Nations International Children's Emergency Fund (UNICEF 2010), about 90 % of the population has access to improved drinking water sources, whereas only 58 % has access to improved sanitation facilities.

25.3 TB and Its Control in Pakistan

TB continues to be a major public health challenge in Pakistan. Each year, an estimated 300,000 new patients are added to the country's escalating TB burden. According to the WHO, the incidence of sputum-positive TB cases in Pakistan is 80/100,000 per year, and the incidence for all types is 177/100,000. The government of Pakistan is committed to meeting all health-associated targets embodied in the Millennium Development Goals (MDGs) and endorsed by the STOP TB Partnership. Pakistan reaffirmed its commitment to TB control in the Medium-Term Development Framework (MTDF) 2005–2010, a national plan guiding annual budgetary allocations for various sectors of the economy including health, and continues to mobilize additional resources to mount a coordinated response against the prevalent but curable disease.

One of the key milestones achieved in Pakistan's fight against TB dates back to 2005, when the NTP, in partnership with its provincial counterparts, achieved 100 % directly observed treatment short course (DOTS) coverage in health facilities within the public sector health delivery system (NTP 2010). This comprises a primary healthcare facility network of 1135 diagnostic centers and more than 5000 treatment centers in the country (UNICEF 2008). This achievement reflected the country's seriousness to reach the targets enshrined in the global Stop TB Strategy, which envisages detection of 70 % of all new Sputum Smear-Positive TB cases and a Treatment Success Rate of at least 85 % (UNICEF 2008).

25.4 Media in Pakistan

Pakistan has a vibrant media landscape; it is among the most dynamic in South Asia. To a large extent, the media enjoys freedom of expression in spite of political pressure and direct bans sometimes administered by political stakeholders. Media has gained repute among masses and has become one of the trustworthy means of information.

Currently, there are 22 media agencies that are on the panel of Ministry of Health. The media agencies have strong public relations with TV, radio, and print media organizations in the country. The media agencies are generally hired to help in designing, planning, and conducting national media campaigns.

Pakistan has 49 television (TV) channels: 15 news channels, 32 primarily entertainment channels, and 2 religious channels. These channels beam soap operas, satire, music programs, films, religious speech, political talk shows, and news of the hour. The antenna-based TV channels are able to reach poor people living in far-flung areas, whereas cable networks target the urban population. Radio is another dominant media, especially in many rural areas. There are more than 40 FM stations reaching millions of Pakistanis both in rural and urban areas.

Print media in Pakistan gets published in more than ten languages, with Urdu, Sindhi, and English predominating. Urdu newspapers are the dominant media in rural areas. They are conservative, folkloristic, religious, and sensational and are by far the most read and influential among the general public. The English media is urban, elite, and more liberal and professional. English print media has an impact among opinion makers, politicians, the business community, and the upper strata of society in general.

25.5 Pakistan Experience of Media and TB

25.5.1 Baseline Assessment Survey

The sole and intrinsic rationale of this extensive tri-fold research survey was to envelop all the possible and prevailing human spheres of society under a well-weaved paradigm that provides objective evidences of their relation with TB (UNICEF 2010). It is clearly evident that the prima fascia of Pakistani society always seems struggling beneath the banner of scores of social, economical, and cultural ailments which are endowed with concrete objective evidences in establishing a relationship between physiological and psychological factors (UNICEF 2010).

A representative sample size was selected focusing ten major cities across country among four provinces and Azad Jammu and Kashmir. The equal distribution formula was adopted in selecting the group of respondents: TB patients (250), doctors (250), and general household (1000).

A qualitative questionnaire was utilized to interview both the TB patients and doctors. Another quantitative questionnaire for general population covered data on five core areas across socioeconomic groups. The areas included: knowledge of TB, healthcare, health-seeking behavior, stigma, and gender.

25.5.1.1 Qualitative Findings

A considerable proportion of TB patients reported initial reluctance to visit the health facility for TB. The reluctance was more related to uncertainties about procedural requirements and facility staff behavior. The doctors reported difficulty in communicating with newly diagnosed patients because of various patient factors (e.g., poverty, psychological condition, fears) and provider factors (time, language, communication tools, etc.) (UNICEF 2010).

25.5.1.2 Quantitative Findings

The proportion of respondents who "ever heard about TB" varied significantly among males and females and across provinces. The general perception was that public health facilities are not well equipped with staff, drugs, and other materials for delivering care. A significant proportion of respondents showed reluctance to visit public health facilities in general. A significant proportion of males (range: 12.6–26.4 %) and females (range: 5.2–41.3 %) were found to have "hidden if infected" in all four provinces and Azad Jammu and Kashmir. Women (both married and unmarried) face more social challenges for accessing the healthcare (UNICEF 2010).

25.5.2 Strategic Planning for Enhanced Communication

The National TB Control Program planned and carried out, with the help of a consultant, the said strategic planning exercise (UNICEF 2010). The early implementation experiences and the baseline survey results were used to inform the decisions made in the strategic planning for enhanced TB control communication. The technical working group process, with the participation of provincial TB control programs and partners, was adopted to develop the national strategic plan for enhanced communication. The strategic plan selects the audience groups and the messages and methods for each target group. The plan delineates the activities, the responsibilities, and also identifies the requirements and cost estimates for various components. This strategic planning on communication enhancement has been done within the framework of overall strategic plan for TB control in Pakistan. This exercise enabled the program to mobilize public and partner (The Global Fund) support for enhanced communication activities, as agreed in the plan (UNICEF 2010).

25.5.3 Media Engagement in Pakistan: A Case Study

Keeping in view the significance of involving media in enhancing the communication for TB control, the Stop TB Partnership Pakistan, in collaboration with NTP, devised a strategy/package for engaging personnel from print and electronic media. The engagement package included the following.

25.5.3.1 Orientation Sessions

A series of orientation sessions, collective as well as one-to-one, were organized. These sessions were to orient the media personnel on the current situation of TB and potential role of partners (including media) in achieving the TB control targets in Pakistan.

25.5.3.2 Consultative Meetings with Editors/Managers

The orientation sessions were followed by group and individual consultative meetings with editors/managers of major national, local, and regional newspapers and magazines as well as TV and radio channels. The objective was to mobilize them for encouraging the staff to write regular articles, reports, and features on TB in order to create an enabling environment to eliminate this disease from Pakistan.

25.5.3.3 Consultative Meetings with Reporters/Marketing Persons

The objective of these meetings was to identify their potential role in TB control and learn how this role can be optimized in Pakistan. One of the main outputs of the consultations was a set of valuable practical suggestions including development of an e-group of health reporters, regular update sharing (with a media fact sheet and brochure developed and newsletters published), and formation of media committees to establish and sustain a viable long-term partnership.

25.5.3.4 Partnership Proposals

Individual proposals from media channels and print media were invited from those who were interested to have a long-term partnership. A total of 4 popular national and regional TV channels, one medical journal and a media production company came up with a list of services in which they were able to offer free of cost or at subsidized rates. These included talk shows, interviews of stakeholders and TB patients, special reports on TB, famous comedy shows, documentaries on TB, musical events at federal, provincial, and district level, TB news on their websites as well as a special space for TB news in their magazines, free articles in medical journals, and fund raising events at national and international levels. To establish viable long-term partnership with selected media partners, the Stop TB Partnership Pakistan signed memorandum of understanding with each selected media partner in the presence of representatives from the WHO, The Global Fund, and the NTP.

25.5.3.5 Support to Media Partners

The TV channels are offered support in the form of commercial air time, i.e., amount for airing of TV Spots with special discounted package as a part of our routine media campaign and press ads for the medical journal. The channels that raise funds for Stop TB Partnership Pakistan will be given an agreed percentage of the raised funds.

Different TV channels were selected while developing media plans for dissemination of TB messages to different target groups. The groups mainly include stakeholders, general public, patients, family treatment supporters, and healthcare providers. Multiple radio channels have also been used to reach various target

groups and publicize important events such as World TB Day and World Health Day. Advertisements and advocacy messages targeting the policy makers and international partners are published in leading English dailies.

25.5.3.6 Expanding Media Engagement

To expand the engagement of electronic and print media in TB control awareness, the district level nongovernment partners were assigned the responsibility to optimize the dissemination of TB messages through local cable networks and enabled grassroot journalists in 57 districts of Pakistan. This expanded media engagement activity at the district level, with the support of The Global Fund, has been a part of implementation of a more holistic set of advocacy, communication, and social mobilization interventions by the respective nongovernment partner. The TB Control Program developed and provided partners a set of standard messages and materials for the district level media engagement process.

The media agencies for TB media campaign are hired though a competitive process. The Expression of Interest (EOI) from the approved media agencies are invited followed by the review of EOIs by a formal committee. The short listed agencies are briefed about the project requirements and are requested to provide technical and financial proposals. The agencies are given at least 15 days to submit these proposals after the orientation meeting. Another Committee then reviewed the technical proposals and short listed three agencies. The three short-listed agencies are then invited to a meeting chaired by the Secretary of Health. The review committee's scoring of the technical and financial bids from each bidder is shared. The media agency is finally selected, on the basis of higher technical competence and lower costs, for the media campaign during the year. The media agency is then given the responsibility for (a) development and production of TV and radio spots, dramas, songs, talk shows, telefilm, scrolls, and educational and promotional materials, and (b) actual implementation of media campaign.

25.5.3.7 Monitoring and Evaluation

The monitoring of media engagement activities at national, provincial, and district levels has been a built-in component of the implementation design. The TV channel and radio engagement is monitored by the NTP through continued screening of media activities and its records. The events with media personnel are monitored primarily on the basis of review of event records, i.e., reports and other support documents (e.g., photos, expense sheets, attendance sheets) and participation in at least a few randomly selected events. The magazines/newspapers are regularly screened and press clippings are compiled. The implementing or media partners also provide pictures, press clippings, and videos of other programs organized for raising awareness.

Modest audience research will measure the impact of the media engagement campaign. The evaluation will comprise mainly of focus group discussions with selected groups of respondents at federal, provincial, and district levels. This will also be supplemented by in-depth interviews with key informants, i.e., stakeholders in the process. The monitoring and evaluation will be coordinated through collaborative efforts of Stop TB Partnership Pakistan and the NTP, and is a principal recipient of The Global Fund Advocacy, Communication, and Social Mobilization (ACSM) grant.

A recently passed resolution by the National Assembly of Pakistan is an example of governments commitment to control and subsequently eliminate the disease as a public health problem, as defined by MDG.

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Chapter 26
The Role of Directly Observed Treatment in the Tuberculosis Epidemic in Beijing

Lixing Zhang and Guangxue He

26.1 Introduction

According to a 1976–1977 survey of Beijing, the conversion rate of newly diagnosed smear-positive tuberculosis (TB) patients to active TB in 1 year was 57.3 % in urban areas and 44.1 % in rural areas. The percentage of people who developed a chronic infection (who shed the bacteria for more than 2 years) was 77.3 % of the total TB patients. This falls very short of designated landmark goals for outpatient treatment established by the International Union Against Tuberculosis and Lung Disease at that time (Fox 1963; Zhang et al. 1980, 1981, 1982a). There many reasons for this shortcoming, but the key issue was patient compliance. Our investigation of the drug use of newly diagnosed patients registered during 1976–1977 showed that in the 3rd, 6th, 9th, and 12th month of the treatment, the percentage of patients who did not adhere to the medication was 25.6 %, 44.6 %, 54.0 %, and 61.7 %, respectively. Of the factors which caused chronic infection, 41.7 % were due to premature withdrawal and 25.6 % were due to irregular consumption of medication in early treatment. The above situation illustrates the severe consequences that are the result of compliance failures in TB patients (Zhang et al. 1980, 1981, 1982a, 1989). To take full advantage of chemotherapy in the control of TB, we must firstly solve the problem of patient compliance. Following the new concept of international TB control, and in combination with the practice of TB control in Beijing, the Beijing TB control policy was formulated in 1983 with three main

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goals: focus on controlling the source of TB infection; widely implement directly observed treatment (DOT); and strongly develop the work of TB control in rural areas.

26.2 The Pilot Program of Directly Observed Treatment

Beijing's TB control implementation met many challenges. At that time, there was no practical experience with DOT in China, especially in rural areas that lacked sufficient medical care. A DOT pilot program was conducted in these rural areas to build understanding of the real situation and explore possible resolutions.

26.2.1 Understanding the Situations of Patients in Rural Areas

In early 1978, Banqiao township (of Beijing's Shunyi county) was selected for a pilot study. Clinicians, along with doctors of Banqiao hospital and rural doctors of the village, visited the TB diagnosed patients one by one. The focus was on assessing the medications taken by patients and the reasons for their irregular compliance. At the same time, an effort was made to understand the work situations of rural doctors, and what could be done to increase compliance among the TB patients. After the preliminary investigation, it was discovered that most patients discontinue treatment without medical consultation because of the easing or disappearance of symptoms or because they didn't understand the need for long-term treatment for TB. Economic factors are a secondary reason for the treatment interruption. Rural doctors and TB patients all lacked knowledge about the appropriate treatment of TB. During the investigation, all of the medical staff were deeply moved by the enthusiasm and work of the rural doctors and the patients' desire to cure TB.

26.2.2 Changing the Ideological Understanding and Medical Behavior

The medical staff always attributes the responsibility for the proper administration of medication to the patients. From the viewpoint of modern public health and TB epidemiology, curing a TB infection can not only reduce the suffering of a patient but can also protect uninfected people from TB infection. Making the chemotherapy regimen clear is not only a good therapeutic measure but can be the main weapon in eliminating TB. Therefore, it is in the interest of public health for the medical staff to assume responsibility for patient compliance rather than to allow patients to take responsibility for their own compliance. The main purpose of the pilot was to affect this change and to increase the enthusiasm of the medical staff. This could lead to a

more active medical staff willing to take initiative to resolve the regular medication problems of patients, take measures to overcome difficulties, and ensure that patients take regular medication. This was called a "revolutionary change" by TB experts at that time. The pilot also sought to strengthen the quality of sputum examination and increase the exam rate, which is the main basis for TB diagnosis, chemotherapy determination, and the monitoring of treatment effects. Another purpose of the pilot was to establish and improve the TB control organizations and to collect data for observed treatment.

26.2.3 Exploring the Feasibility of Directly Observed Treatment

First, it was important to make it clear that directly observed treatment is the main focus of TB management. Second, the main subjects for DOT should be smear-positive cases at the beginning of treatment. Observed treatment should require the regular dosing of medication and make it convenient for patients to take their medication. At that time, the growth of rural "barefoot doctors" created favorable conditions for the development of DOT. After their training, the enthusiastic barefoot doctors encountered 1–2 smear-positive patients in each village. After consulting with the patients and contracting a treatment agreement, they persuaded most of the patients to take medicine in the village clinic. Drugs stored in the village clinics were secured by the barefoot doctors. It was a requirement to make a record on the supervision card after each treatment. An important finding in the pilot was the emphasis on remedial measures taken by barefoot doctors if the patients did not take medication on time. Another important consideration was to make sure the rural hospitals had a well-defined person responsible for inspection to visit village clinics or patients on a weekly basis.

26.2.4 Achievement of Significant Results

After the pilot in Banqiao township of Shunyi county, the pilot scope was gradually expanded to the whole of Shunyi county and part of Daxing county, including about 770,000 people across 44 townships and 808 villages. After practicing DOT for 1 year, the program was evaluated in 208 patients who had received treatment for 7 months to 1 year. The program was assessed by measuring two indicators: the rate of patient adherence to medication and the patient cooperation rate.

$$\text{Rate of patient adherence} = \frac{\text{actual medication amount taken per patient}}{\text{medication amount received per patient}} \times 100$$

Table 26.1 DOT of TB patients in Beijing pilot areas in 1977 (Beijing TB Center data)

The status of patients	Cases	Actual number of medication doses taken	Medication doses received	Medication adherence rate (%)
Patients shedding bacteria	116	12,424	12,468	99.6
Patients not shedding bacteria	92	7615	7647	99.6
Total	208	20,039	20,115	99.6

$$\text{Patient cooperation rate} = \frac{\#\text{ of patients who adhere to}\left(98-100\right)\%\text{ of medication amount}}{\text{number of patients who should be treated}} \times 100$$

The rate of patient adherence to medication was as high as 99.6 % (see Table 26.1).

The cooperation rate of patients shedding bacteria was as high as 95.6 %; among these patients, the rate without treatment interruption was 92.3 %. Treatment interruption consisting of 1–2 times accounted for 3.4 %, and treatment interruption consisting of three times or more accounted for only 4.3 %. This was a very satisfactory achievement.

The treatment therapy at that time was a 12-month regimen of streptomycin (S) and isoniazid (H): $1SH/11S_2H_2$. After 1 year of treatment, the sputum-negative conversion rate of the 104 smear-positive drug-sensitive patients was 98.1 %, and the recurrence rate was 2.1 % in the first year (Zhang et al. 1980, 1981, 1982a, 1989).

After the success of the pilot, conclusions continue to be drawn, especially to facilitate the solution of various problems encountered in the implementation of DOT and to continue to explore ways and means to solve problems in the pilot area.

26.3 Expansion and Implementation of Directly Observed Treatment

The implementation of DOT is a feat of logistics requiring financial investment, government's commitment, technical specifications, and the organization and oversight to establish and perfect staff training.

26.3.1 In-Depth Training for Modern TB Control

To carry out directly observed treatment successfully, firstly the appropriate knowledge must be transferred. The education of medical staff about the concept and practice of modern TB control is crucial in the implementation of DOT. Since 1979, Beijing Research Institute for Tuberculosis Control trained all levels of health

Table 26.2 Annual training overview of the city's professional TB doctors (1979–2000, Beijing TB Center data)

Training content	Times/year	Participants
Symposium of TB control with the actual situation of Beijing	2	The district and country directors of institutes for TB control
Academic progress of modern TB control	6	All levels of anti-TB doctors in Beijing
Seminar of the quality control of *Mycobacterium tuberculosis* examination in sputum	1–2	Inspectors of every institute for TB control and some general hospitals
Seminar of TB supervision and center registration	1	Relevant personnel of every institute of TB control
Courses on BCG vaccination	1	Staff of BCG office in every institute of TB control
Training of diagnosis and identification of pulmonary TB	1	Doctors in institutes of TB control
Classes of modern TB control	1	All new doctors and nurses in institutes of TB control

Table 26.3 Training schedule of part-time anti-TB doctors in townships and villages of Beijing rural areas (1997–2000, Beijing TB Center data)

	Anti-TB doctors in townships		Anti-TB doctors in villages	
Number of trainings attended	Number	%	Number	%
0	2	0.8	656	18.0
1–4	69	28.3	1238	34.0
5–9	80	32.8	1249	34.3
10	93	38.1	500	13.7
Total	244	100	3643	100

personnel multiple times to familiarize them with the knowledge and skills of modern TB control. The annual training courses from 1979 to 2000 are shown in Tables 26.2 and 26.3.

26.3.2 Establishment and Improvement of the TB Control Network

Beijing has established 18 administrative regions, including four downtowns, four suburban areas, and ten rural counties. In 2000, the population of Beijing was about 12 million, 42 % of which was a rural population. TB control organizations must guarantee the smooth implementation and development of control measures in a variety of conditions. To implement DOT, the patient's medication needs must be conveniently met. At the same time, the city's TB control network should be

gradually established and improved under the leadership of health administrations at all levels according to local medical staff resources and networks of medical health care. The Beijing Tuberculosis Prevention and Cure Institution (now the Beijing Research Institute for Tuberculosis Control), a central institution established in 1952, was responsible for planning, design, implementation, personnel, quality monitoring, and central registration of DOT. Eighteen districts and counties had their own TB prevention and cure institutions, responsible for the TB control of about 200,000–500,000 people. In rural areas, DOT was included in the county's primary health care network under the direction of the county's TB prevention and cure institutions. Ten counties (240 towns, 10,000–25,000 people per town) all had full-time or part-time TB control doctors. TB control was added as a responsibility in the county health centers. Ten counties (with 3573 administrative villages and 1000–2000 people per village) set up village health centers with 3664 village doctors who joined in the training of TB control, transferred suspected TB patients, and supervised the treatment of smear-positive patients. Establishing TB protection networks in the city, districts, counties, and villages is an important measure to develop and implement the directly observed treatment.

26.3.3 Active and Firm Implementation of the Directly Observed Treatment

Based on the success of the pilot and whether the conditions were appropriate for DOT in a given district or county, Beijing implemented DOT gradually and firmly. Otherwise, counties were helped to solve problems standing in the way of implementing DOT. Basic conditions necessary to begin implementing DOT were as follows:

- There were TB prevention and cure organizations in every district or county.
- Professional TB prevention institutions served as the work centers for the implementation of the directly observed chemotherapy under full supervision. These institutions had the ability to make plans for local projects and to organize personnel training, had the technology and equipment to make diagnosis and treatments, and had reliable technology for TB examination and statistical work.
- There was a sound TB prevention and treatment network which could bring DOT into practice, combine professional medical staff with various medical resources, and establish a series of corresponding administrative measures.

After launching in 1984, it took about 4 years to accomplish DOT coverage in 18 counties in Beijing. "Coverage" means that the smear-positive patients citywide accepted DOT. The coverage rate increased from 30 % in 1979 to 81 % in 1984 and reached above 90 % in 1990 (see Table 26.4).

Table 26.4 DOT coverage for new smear-positive cases and quality control by random visits to health posts and patients' homes in Beijing, 1978–1996 (Zhang et al. 2000a)

Year	DOT coverage (%)	Completion of full duration of DOT (%)	DOT cases visited (%)	True compliance with DOT in visited cases (%)
1978	10			
1979	30			
1980	45			
1981	62			
1982	76			
1983	75			
1984	81	92		
1985	63	92		
1986	70	89		
1987	78	90		
1988	87	87		
1989	87	88		
1990	93	92	65.6	96.6
1991	97	95	81.5	99.1
1992	98	96	73.6	99.0
1993	98	96	73.5	99.0
1994	97	94	73.1	99.7
1995	96	91	70.3	98.5
1996	91	90	67.0	98.0
1997	87	87		
1998	89	89		
1999	91	89		
2000	92	89		
2001	92	92		
2002	95	86		

26.3.4 Establishment of Technical Policy and Institution

The key issue for successful DOT is strictly implementing standardized TB guidelines and technical policy and insuring technical policy is acceptable and feasible.

26.3.4.1 The Procedure of the Observed Treatment of Patients

Guidelines and education: Patients should receive guidelines and education for about 20 min before beginning the DOT regimen. This allows patients to realize the importance of medication compliance, including why patients need directly observed treatment and must accomplish the full course of chemotherapy and other basic knowledge.

Determine the supervisor, address, and time for the observed treatment: It is important to identify a supervisor and to ensure that it is convenient for patients to receive supervised medication. Normally, rural doctors are responsible for supervising the administration of medication. If patients do not come to take medicine on a given day, a village doctor must take the corresponding remedial measures to ensure the patient takes the medicine on that day. Before patients go home, they should get in touch with the supervisor and ensure that they receive medicine on time. It is emphasized that medicine should be placed in village clinics, and the medicine record card should be filled out after medication.

Step-by-step supervision: Medical staff in district and county hospitals should visit and supervise the patients 1 week after diagnosis, normally verifying the drug dose, making a record on the medicine card, and enquiring of patients and village doctors. Later, the visits can be once a month. Staff from rural health clinics should visit village doctors and patients every 2 weeks.

26.3.4.2 Formulation of Uniform Standard Intermittent Protocol

Before 1979, the TB treatment therapies in Beijing were very confusing and disorganized. Beginning that year, it was considered necessary to establish a uniform standard protocol. This protocol should be effective, have minimal side effects, be affordable, and have adequate local supply. Patients should also be willing to accept the protocol. Once a therapy is formulated, it must pass through rigorous scientific practice and prove to be effective before it can be confirmed to be a uniform standard treatment. Due to the new understanding of the chemotherapy mechanism of TB, the regimen of $1SH/11S_2H_2$ therapy was used (0.75 g S and 300 mg H daily, with the dosage increased to 1.0 g S and 700 mg H in the intermittent phase). This chemotherapy was proven to be effective by scientific research.

26.3.4.3 Support from Health Administrative Leadership

The achievement of the pilot was summarized with investment–benefit analysis, and, striving for the support from all levels, it was reported to the health bureaus in Beijing's municipalities, districts, and counties that directly observed chemotherapy was highly effective. Since 1979, the Beijing Municipal Health Bureau allocated 100,000 RMB ($15,625 in today's US dollars) to help TB patients in financial difficulties. Beijing's standard chemotherapy for initially treated smear-positive patients ($1SH/11S_2H_2$) costs 33 RMB (~$5) a year for one patient and 10,000 RMB (~$1500) for 3030 patients. In fact, Beijing didn't have so many initial treated patients who shed bacteria for 1 year. For full use of this fund, relief measures of anti-TB drugs were formulated in Beijing. The fund was increased in subsequent years, and free drugs were supplied to expanding categories of patients.

26.3.4.4 Enhancement of Quality Control

Quality control was the key point in the implementation and expansion of directly observed treatment. The following measures were taken:

Hospital director's responsibility: TB hospital directors of every district or county were encouraged to explore suitable methods for the actual local situation. This was an important aspect for sustainable development of DOT. At the same time, the performance of the directors was linked to the achievement of DOT.

Strengthening the supervision: Beijing Research Institute for TB control set up a special department responsible for DOT in the entire city. Medical staff went directly to patients' homes in each district and county to supervise the DOT. They were requested to randomly visit at least 50 % of the registered smear-positive patients every year and check up on the compliance of medication. In 1990, more than 65.6 % of the initial treated smear-positive patients had been visited, and in 1991 this number rose to 81.5 %. In 1990, the completion rate of the DOT was emphasized, which led to strict accounting of patient's medication times during the whole treatment. This measure played a positive role in improving DOT completion, and over 95 % of patients completed the whole course (see Table 26.1).

Assessment of implementation: Meetings attended by the directors of city, district, and county health bureaus and the TB control institutions were convened twice a year to summarize the observed treatment, announce the specific situations in each district and county, and identify problems and propose solutions.

26.4 The Role of Directly Observed Treatment in the TB Epidemic in Beijing

Since directly observed treatment has been strictly implemented in Beijing over a long period of time, there is an extensive set of long-term epidemiological data available. In that period, Beijing met the basic requirement to evaluate the role of DOT in TB epidemiology. HIV infection played little impact on Beijing's TB epidemic.

26.4.1 The Role of Directly Observed Treatment in the Prevalence of TB Infection and Annual Risk of TB Infection

The goal of TB control is to limit TB infection. Only when the TB infection is reduced can TB be eventually eliminated. Estimating the annual risk of tuberculosis infection (ARTI) from the prevalence of TB infection is not only a reliable indicator to evaluate TB epidemic situation (Bleiker et al. 1989; Arnadottir et al. 1996), but it

Table 26.5 The DOTS coverage rate, the DOTS compliance rate, and the cure rate of newly registered smear-positive patients in Shunyi district, Beijing (Zhang et al. 2000b)

Year	Patients	DOTS coverage rate	DOTS compliance rate[a]	Cure rate (%)
1987	186	97.2	92.1	92.5
1988	132	90.1	99.0	90.9
1989	109	94.4	98.8	90.9
1990	159	99.2	96.6	91.2
1991	120	99.1	98.1	95.0
1992	120	92.0	90.3	89.2
1993	96	93.1	95.5	90.6
1994	79	97.1	97.1	91.1
1995	93	94.4	92.7	87.1

[a]DOTS compliance rate refers to the percentage of patients who complete the DOTS in the whole course

can also be used to assess the role of measures. In recent years, researchers are trying some new methods to distinguish between natural TB infection and BCG vaccination. As BCG vaccination becomes more widespread, it becomes more difficult to get reliable ARTI data. To overcome this challenge, Beijing Research Institute for Tuberculosis Control cooperated with the International Union Against Tuberculosis and Lung Disease (The Union) and the KNCV Tuberculosis Foundation's Tuberculosis Surveillance Research Unit (TSRU, The Hague, The Netherlands). In 1987, a region was selected where DOTS had been well implemented and then neonatal BCG vaccination was halted. Then an international unified approach was taken to conduct tuberculin testing on the non-vaccinated children aged 6–7 (first grade) to determine the TB infection rate (Zhang et al. 2000b).

In 1988, Shunyi District in Beijing, with a population of 498,549, was chosen for a pilot program. A series of precautionary measures had been taken there, particularly to regulate the implementation of DOTS which had been introduced in this area in 1978. The DOTS coverage rate had reached 90 % or more in 1987. The DOTS compliance rate (the percentage of patients who complete DOTS in the whole course of treatment) was more than 90 %, and the cure rate was more than 87 % (see Table 26.5). Children born in 1988 and 1989 (age 6–7) and not BCG vaccinated were included in the 14,420 students entering the first grade in the fall of 1995. Of these, 14,127 (98 %) received the tuberculin test and had an average age of 7.2 years. A total of 12,836 (91 %) of the students had a vaccination record confirming the lack of BCG vaccination. The 174 students with a tuberculin test result of 10 mm or above were considered to be infected with TB. Figure 26.1 shows that in BCG-non-vaccinated children, the distribution of duration showed clear bimodal features. In BCG-vaccinated children, the distribution of duration doesn't have this feature, but has peaks at 5, 10, and 20 mm. The TB infection rate was 1.4 % (95 % CI: 1.2–1.6 %). ARTI was estimated to be 0.19 % (95 % CI: 0.16–0.22 %). It was only known that the TB infection rate of children aged 7 in Beijing was 35 % in 1950. During the 45 years from 1950 to 1995, the TB infection rate was reduced from 35 to 1.4 %, with an average annual decline rate of about 8 %. ARTI dropped

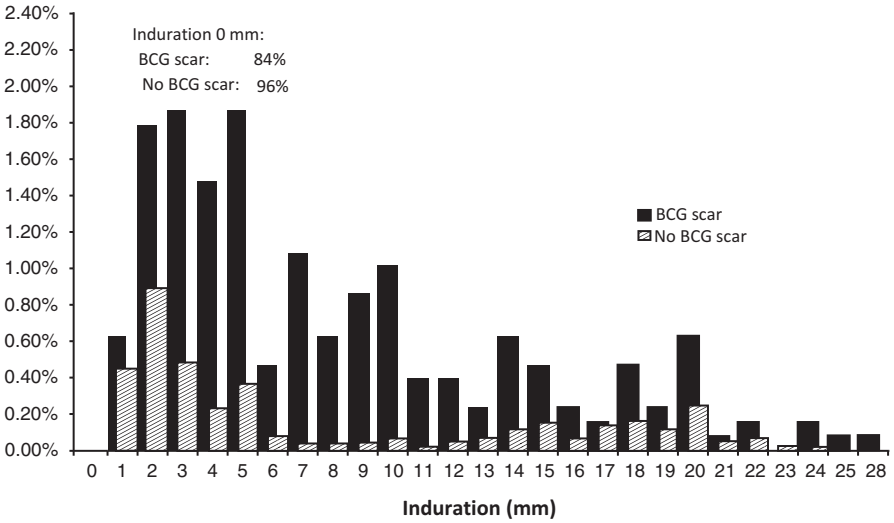

Fig. 26.1 Frequency distribution of tuberculin skin test results (greatest transverse diameter of induration in millimeters) in children with and without BCG scars in Shunyi County, 1995 (Zhang et al. 2000b)

from 5.8 % in 1950 to 0.19 % in 1995. An ARTI of 1.0 % was thought to be indicative of a serious TB epidemic in 1995; an ARTI of 0.19 % was thought to be a less serious problem. This pilot showed that only 2 per 1000 children were infected with TB in the 7 years from 1988 to 1995, indicating a very slow spread of TB. Though 1094 smear-positive pulmonary TB patients were discovered in this 7-year period, these TB-infected cases received DOT in a timely fashion and soon lost their infectiousness. This reflects the significant role of DOT in reducing the TB infection and ARTI (Zhang et al. 1982b, 2000b).

26.4.2 The Role of Directly Observed Treatment in the Transmission Parameter in the Population of TB Patients

TB transmission parameter ("contagious" parameter) refers to the average number of healthy people who had not been infected with TB and were finally infected by source of infection in 1 year. The calculation of TB transmission parameters derives from the annual TB infection rate. The formula (from Styblo 1984) is:

$$\text{Transmission parameter} = \frac{\text{ATRI}\left(\text{per}\,10,000\right)}{\text{prevalence of infectious TB}\left(\text{per}\,10,000\right)}$$

Table 26.6 Death rate, estimated prevalence of infectious source, annual infection rate, and contagious parameter (Styblo 1984)

Year[a]	Death rate per 10,000 [A]	Estimated prevalence of infectious source per 10,000[b] [4 × A]	Annual infection rate per 10,000 [B]	# of infections caused by 1 source per year (contagious parameter) [B/(4 × A)]
1922	11.5	46.0	602	13.1
1925	10.0	40.0	513	12.8
1928	8.8	35.2	437	12.4
1931	7.1	28.4	372	13.1
1934	5.6	22.4	316	14.1
1937	14.8	19.2	269	14.0
1921–1938				13.2

[a]1922: average for 1921–1923, 1925:1924–1926, etc.
[b]Assumed ratio between prevalence of infectious source and death rate 4:1

Table 26.7 Relationship between the annual TB infection rates and the prevalence of smear-positive cases of pulmonary TB in Lesotho and Uganda (Styblo 1984)

Country	Survey years	Annual risk of TB infection at age 10 years per 10,000 (in 1960)	Prevalence of smear-positive cases of pulmonary TB per 10,000 (all ages)	Ratio of infections per prevalence of smear-positive cases
Lesotho	1957, 1962–1964	410.0	30.0	13.7
Uganda	1958, 1971–1972	220.0	21.6	10.2

Table 26.8 Infectious TB prevalence and transmission parameters per year in Shunyi District, Beijing, from 1991 to 1992 (He 2002)

Year	Infectious TB registration rate (per 100,000) [A]	Prevalence of infectious TB (per 100,000) [B] = [A]/70 %	Annual risk of TB infection (%) [C]	TB transmission parameters = [C]/[B] × 1000
1991	23.2	33.6	0.21	6.3
1992	23	32.9	0.21	6.4
Average	23.1	33.2	0.21	6.3

TB transmission parameters were firstly proposed by Styblo. Based on his calculation of TB in the Netherlands during 1922–1938 and the survey during 1957–1972 in Lesotho and Uganda (see Tables 26.6 and 26.7), he concluded that one untreated source of infection can infect 10–15 healthy people in 1 year (Styblo 1984).

Reliable prevalence of TB infection is the key point to estimate the annual risk of TB infection. Obtaining the annual risk of TB infection in children aged 7 and the local TB prevalence adopted from the pilot in Shunyi District, Beijing, in 1995, we calculated that the transmission parameter was 6 (see Table 26.8). It indicated that the implementation of the directly observed treatment can reduce the number of healthy people infected by one source of TB from 10–15 to 6 (Styblo 1984; Zhang et al. 2000b; He 2002).

Because the patients come to see the doctor after the appearance of TB symptoms, there is a delay in diagnosis and treatment, and the infection of patients occurs mainly before diagnosis and chemotherapy (Zhang et al. 1982b). With the transmission parameter falling to 6, we can logically reason that these six people were possibly infected before the diagnosis and treatment of the TB patient. This illustrates that DOT plays an important role in reducing the TB infectiousness (Styblo 1984; Zhang et al. 2000b; He 2002).

26.4.3 The Impact of Directly Observed Treatment on TB Prevalence

TB patients mainly include newly diagnosed patients and relapsed cases. After the standardization of DOT, TB prevalence declined rapidly and significantly. Generally, with the improvement of DOTS coverage, the treatment success rate increases and the prevalence decreases significantly. For example, when DOTS was started in Beijing in 1978, the coverage was only 10 % and gradually increased to 93 % in 1990. From the Beijing sampling results in the national survey of TB epidemiology, we can find that the prevalence of smear-positive TB decreased from 127/100,000 in 1979 to 16/100,000 in 1990, with a decrease of 87.4 % and an average annual decline of 17.2 %. Retreatment cases also decreased significantly, from 28.9/100,000 in 1979 to 2.6/100,000 in 1990, with a decrease of 91.0 % and an average annual decline of 19.7 %. Due to TB control work, the average annual decline rates of TB prevalence and retreatment cases were high (see Table 26.9; Zhang et al. 1989, 2000b; Zhang and Kan 1992; Ministry of Health of the People's Republic of China 2003).

26.4.4 Impact of DOT on the Incidence of TB

In the regions with good TB registration reports, we can use newly registered TB cases to reflect the trend of TB incidence. The newly registered smear-positive TB cases were stable during 1980–1987. It increased in the beginning of DOT use, but continued to decline after 1987 from 18.9/100,000 in 1986 to 7.3/100,000 in 1996, with an annual decline rate of 9.1 % (see Table 26.10).

Of greater significance was the fact that the epidemiology of TB showed that the TB situation in Beijing was greatly improving: the TB onset age declined, the incidence in children and adolescents was significantly reduced, but the incidence in elderly increased. The average annual decline rates of newly registered smear-positive cases were 7.8 %, 5.7 %, and 0.8 %, respectively, in the 0–14, 15–29, and 30–49 age groups during 1981–1997. The 50 and above age group had an average annual decline rate of 0.7 % (see Table 26.11).

Table 26.9 The prevalence trend of smear-positive pulmonary TB and chronic cases registered in Beijing 1979–1990 (Zhang et al. 2000a)

Year	Prevalence survey rate/100,000	Mean trend %/year	Retreatment cases rate/100,000	Mean trend %/year	DOT coverage (%)
1979	127		28.9		30
1984/1985	56	−12.8	No data		63
1990	16	−22.2	2.6	−19.7	93
% reduction	87.4	−17.2	91	−19.7	

Table 26.10 Trends in newly registered smear-positive pulmonary TB cases and TB meningitis in children in Beijing, 1980–1996 (Zhang et al. 2000a)

Year	Newly registered smear-positive cases			DOT coverage (%)
	Cases	Rate/100,000	Mean trend %/year	
1980	1346	15.2		45
1981	1425	15.8		62
1982	1692	18.6	5.8	76
1983	1652	17.8	8.0	75
1984	1851	19.7	3.3	81
1985	1945	20.4	2.3	63
1986	1823	18.9	−2.0	70
1987	1808	18.5	−9.8	78
1988	1473	14.8	−13.7	87
1989	1210	12.0	−9.9	87
1990	1346	13.1	−6.5	93
1991	1220	11.8	−8.4	97
1992	923	8.9	−17.5	98
1993	764	7.3	−13.7	98
1994	785	7.4	−4.2	97
1995	891	7.7	0.1	96
1996	780	7.3		91
1986–1996			−9.1	

Table 26.11 Trends of newly registered smear-positive cases by age group, Beijing, 1980–1997 (Zhang et al. 2000a)

Age group (years)	Year			Reduction (%) since 1980	1997 average annual reduction (%)
	1980	1990	1997		
0–14	1.2	0.3	0.3	75.0	7.8
15–29	22.4	16.9	8.3	62.9	5.7
30–49	13.1	12.2	11.4	13.0	0.8
50+	22.6	31.5	25.6	−13.2	−0.7

Table 26.12 Trends of initially resistant anti-TB drugs in Beijing, 1978–1996 (Zhang et al. 2000a)

Period	Initial drug resistance (%)				
	INH	SM	RMP	EMB	INH + RMP
1978–1979	13.9	12.3			
1981–1982	7.8	10.8	0.4	0.4	0.4
1983–1984	11.6	11.3	0.3	0.7	0.3
1985–1986	10.0	12.7	1.2	0.4	0.0
1987–1988	8.1	7.3	2.4	1.6	1.6
1989–1990	3.9	5.8	1.9	0.6	0.0
1991–1992	6.8	4.2	1.7	1.7	0.0
1995	5.4	6.0	2.7	1.3	0.7
1996	4.2	5.8	2.5	0.8	0.8

INH isoniazid, *SM* streptomycin, *RMP* rifampicin, *EMB* ethambutol

26.4.5 Impact of DOT on the Initial Drug Resistance of TB

Canetti et al. (1969) pointed out that initial drug resistance reflected the quality of treatment for smear-positive patients and high initial drug resistance must be caused by poor TB treatment measures. Conversely, low initial drug resistance was the result of successful TB treatment. Beijing did not have efficient treatment measures before 1978. Since the implementation of DOT after 1978, the coverage of DOTS and the cure rate of newly registered smear-positive TB patients have increased and the TB initial drug resistance decreased annually after about 10 years. The initial drug resistance of isoniazid (INH) and streptomycin (SM) decreased from 13.9 % and 12.3 % in 1978–1979 to 4.2 % and 5.8 %, respectively, in 1996 (Canetti et al. 1969; Zhang and Kan 1992; Zhang et al. 1995; Zhang 2004). The initial drug resistance of rifampicin (RMP) started low and increased later. On the other hand, the multidrug resistance of RMP and INH was low (see Table 26.12).

26.4.6 Impact of DOT on TB Mortality Rates

Statistics of TB mortality were determined over the past 40 years. TB mortality decreased before implementation of directly observed treatment, but DOT further accelerated this trend. After the implementation of DOT in Beijing, the average annual TB mortality between 1965 and 1975 declined at a rate of 3 % per year. In 1980, the annual rate of decline of TB mortality went up to above 7 % (see Table 26.13).

From the data in Tables 26.10 and 26.13, we can see that the directly observed treatment plays a significant role in the epidemiology of TB. However, the speed and extent of the role it plays varies with various epidemiological indicators.

Table 26.13 Trend in TB mortality in Beijing 1965–2000 (Zhang et al. 2000a)

Year	Mortality/100,000	Trend (%)	Mean trend % per year	DOT coverage (%)
1965	24.9			
1975	17.6	−29.3	−2.9	
1980	11.2	−36.4	−7.3	45
1985	6.6	−41.1	−8.2	63
1990	4.2	−36.4	−7.3	93
1995	2.6	−38.1	−7.6	96
2000	1.8	−30.0	−7.1	92
1965–2000		−92.8	−7.5	

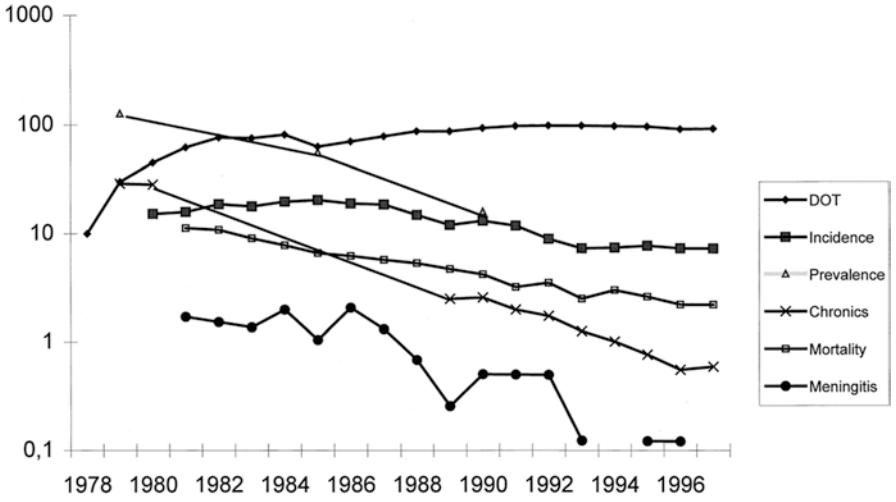

Fig. 26.2 The association of TB indices in Beijing, 1978–1996 in cases per 100,000 (Beijing TB Center data)

As DOT mainly controls the source of TB infection and directly improves the TB cure rate, the TB prevalence rate drops quickly. The improved coverage of DOT and the rapid decline of TB prevalence are inversely related (see Fig. 26.2). The prevalence of the retreatment patients declined dramatically. This is mainly because of the early implementation of the rifampicin therapy for the retreatment patients in Beijing (1980). The effect of DOT on ARTI is significant and can also reduce the initial resistance and mortality. As the TB incidence is influenced by the pathogenesis, DOTS can reduce the new infection and exogenous reinfection indirectly, but it has very little effect on the endogenous reactivation. Ten years after the implementation of the DOT, the registration rate of smear-positive TB cases began to decline, with the greatest reduction in children and young people. This was obviously related to the reduction of new TB infections (see Figs. 26.2 and 26.3).

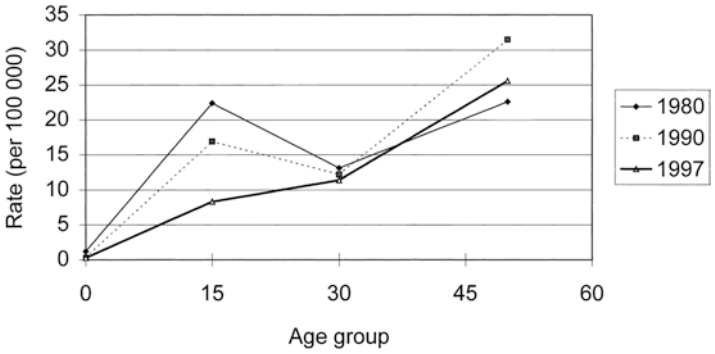

Fig. 26.3 Trend in notification of newly diagnosed sputum smear-positive TB in Beijing by age group, 1980–1997 (Beijing TB Center data)

26.5 The Limitations of DOT in Combating the TB Epidemic

DOT does not affect those with latent TB infection, which accounts for a large proportion in developing countries and 44.5 % in China (Ministry of Health of the People's Republic of China 2003). This group may develop TB at any time in their lifetime (many decades down the line) due to various factors independent of DOT. It requires long-term effort to implement DOT alone and several generations of work to control the TB epidemic. Therefore, concurrently with the implementation of DOT, research should be done on new measures to prevent TB infection of uninfected people and deal with the onset of infected populations, including vaccines to prevent new infections as well as the incidence of infected groups. New comprehensive interventions are the best tools for TB control.

There are many influencing factors for long-term implementation of DOT: geography, population, nationality, culture and religion, social economy, disaster, war, politics, medical institution, and some unexpected events. These factors impede the long-term implementation of DOT (Zhang 2004).

The benefit of DOT is restricted to the current technologies of diagnosis and treatment. With the lack of early diagnostic techniques, many healthy people have been infected for some time before being diagnosed by most of the current diagnostic methods. Long treatment time, few effective drugs, and numerous side effects bring many difficulties to DOT implementation. If we can find better diagnostic techniques and more specific treatments to shorten the treatment time, the benefit of implementing and maintaining DOT programs will increase.

The limitations of DOT are mainly that it has no effect on the TB infection group, and it is influenced by many factors that make long-term implementation difficult. Directly observed treatment aims to manage the source of TB infection. If successful, DOT will directly lower the TB prevalence, TB infection rate, TB mortality, and drug resistance rate, while indirectly reducing TB incidence.

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Chapter 27
The Promise of New TB Vaccines

Michael J. Brennan, Lewellys F. Barker, and Thomas Evans

27.1 Background

Tuberculosis (TB) remains a significant cause of morbidity and mortality despite global efforts to impede its impact. It is clear that new tools, including diagnostics, drugs, and vaccines, will be required to treat and control TB and halt the global pandemic (Barker et al. 2009; Brennan and Thole 2012). Bacillus Calmette–Guérin (BCG) vaccine is widely administered in most areas endemic for TB; it is the only vaccine available to protect against TB. After its introduction in Paris in 1921, BCG (Calmette 1931), a live attenuated strain of *Mycobacterium bovis*, was distributed to many laboratories around the world and maintained for decades by numerous serial passages. Accordingly, there are now a number of BCG substrains that exhibit striking genotypic and phenotypic heterogeneity (Behr and Small 1999; Behr 2002; Corbel et al. 2004).

BCG has been shown in multiple case–control studies to be effective in children for the prevention of more serious forms of TB, such as tuberculous meningitis and miliary TB (Rodrigues et al. 1993). However, a systematic review of data from clinical trials suggests that the protective efficacy of the vaccine is highly variable in adults and ranges from 0 to 80 % (Colditz et al. 1994, 1995). For example, in two large randomized controlled trials (RCT) where BCG or placebo was given to 3005 1–19-year-olds in studies performed in native American populations in the USA (Aronson et al. 1958) or to 26,267 14–15-years-old adolescents in studies done in the UK (Fourth Report of Medical Research Council 1972), 70–80 % protection was observed vs. childhood and adult pulmonary TB in vaccines. In another very large RCT in the south of India, which enrolled 286,161 1–20-year-olds, there was limited protection in the youngest age cohort and none in adults or overall (Datta et al. 1999). A number of explanations have been proposed for the variable

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performance of BCG in different trials. These include, among others, the variation in BCG strains, variable background infection with environmental mycobacteria which can interfere with BCG, differences in strains of *Mycobacterium tuberculosis* (*Mtb*) causing TB disease, intensity of *Mtb* exposure, age of vaccines, and variable susceptibility of different populations to TB. These findings highlight the need for a new TB vaccine, particularly one that effectively prevents transmission, to aid in the control of the global TB epidemic which has been worsened by the AIDS pandemic and by increasing antibiotic resistance in *Mtb* strains.

Until recently, the WHO recommended BCG administration to all newborns as close to birth as possible as part of the Expanded Program on Immunization. This has been the standard practice in many counties for a number of decades (Zwerling et al. 2011). It is estimated that approximately 100 million infants receive BCG every year, yet despite this widespread use, the highest burden of TB disease remains in the very countries where BCG immunization of infants is routinely practiced. Reports of serious complications of BCG use were relatively uncommon in the past and related to specific BCG substrains or largely confined to infants with congenital immunodeficiencies (Lotte et al. 1988). Recent reports from Argentina and South Africa of disseminated BCG disease in as many as 1 % of infants infected with HIV caused the WHO to change its blanket recommendation of universal BCG vaccination to one excluding infants infected with HIV (Hesseling and Gie 2007). Accordingly, there are current efforts to improve BCG or to develop an alternative priming vaccine or vaccine regimen that is both safer and more effective than current BCG.

The current mission of the TB vaccine community is to develop effective TB vaccines to prevent TB across all age groups in an affordable and sustainable manner. This is a daunting task, but recent advances in TB research have provided new antigens to use in vaccine candidates, more rigorous animal models for preclinical studies of new investigational TB vaccines, innovative immunological methods for measuring host immune responses, and novel vaccine techniques for delivering vaccines to all populations needing protection against TB (especially including those that are hard to reach in high-burden countries). However, a number of critical scientific research questions need to be addressed in order to instruct the TB vaccine field and accelerate vaccine development. These include identifying correlates of vaccine-induced protective immunity that would facilitate preclinical and clinical testing of new vaccines. At a minimum, we need to understand the human immune responses required for natural resistance to TB infection and those responses associated with progression from latency to reactivation disease. There is a renewed interest within academic research institutes and other organizations to address these key scientific questions required to identify and develop new safe and effective TB vaccines. Nonprofit product development organizations, particularly Aeras (http://www.aeras.org/home/home.php) and the TuBerculosis Vaccine Initiative (http://www.tbvi.eu/), have been launched over the past decade to coordinate and facilitate research, clinical testing, and introduction of new TB vaccines. These organizations work with the support of international stakeholders such as the Bill & Melinda Gates Foundation, the Wellcome Trust, the US National Institutes of Health, the European Community (e.g., The Netherlands and UK), the World Health Organization (WHO), the Stop TB Partnership, and partners in the pharmaceutical and biotech industries.

27.2 Clinical Advances over the Last Decade

Most successful vaccines available today induce antibody-mediated immunity but, as demonstrated in numerous animal studies (Baldwin et al. 1998; Chambers et al. 2001; Chen et al. 2009; McMurray 2001), a robust TH1 cellular immune response, possibly accompanied by antibodies, is likely be required for protection against TB infection. Therefore, most vaccine candidates currently under study contain various combinations of vectors, adjuvants, and antigens that induce classical TH1 CD4 and CD8 T cell responses and cytokines such as IFN-γ and TNF-α. Over the past decade, 14 candidates containing a variety of *Mtb* antigens that stimulate T cell responses have moved forward into human clinical studies. Figure 27.1 shows the new TB vaccines that are in various phases of clinical trials. The figure demonstrates that there are different categories of vaccines including inactivated whole cell or whole-cell extracts (*M. vaccae*, DAR 901, and RUTI), viral-vectored vaccines (MVA85A, AERAS-402, Crucell Ad35, TB/Flu-04L, and AdAg85A), fusion protein subunits with adjuvants (M72/AS01, Hybrid 1/IC31, Hybrid 4/IC31, H56/IC31, and ID93/GLA SE), and live recombinant vaccines (VPM 1002and MTBVAC). DNA vaccines against TB are being developed in China, Brazil, and elsewhere (Li et al. 2006), but have not yet entered into human clinical trials. These recent clinical trials of new TB vaccines have included populations such as naïve adults and infants, the latently infected (TST+ or IGRA+), and HIV+ adults; the data are informing the field with safety and immunological profiles. Because BCG vaccine is used in many nations at or close to birth, most of the new viral vectored and adjuvanted fusion protein subunit vaccines are being studied for use as a booster vaccine following BCG vaccination. Recombinant BCG vaccines are being studied as licensed BCG replacement vaccines with key goals of being safe for use in populations at risk for HIV, more long-lived efficacy, and better priming for subsequent boosting with other candidates. Results from phase IIb trials will hopefully provide information on the possible efficacy of vaccines that induce CD4 (e.g., MVA vectored) or CD8 (e.g., adenovirus vectored). In certain populations, such trials will inform the design of future phase III trials. At this time, the subject numbers are too small for licensure of a new product, but more trials will guide the design of future phase III trials. Ideally, phase III studies will be multicenter studies performed in various regions (including Africa, Asia, and the Americas) in order to analyze potential differences in the immunological variability in global communities as well as assess the vaccines' ability to protect against different circulating *Mtb* strains.

Most clinical studies to date in high-burden countries have been performed in sub-Saharan Africa. Significant accomplishments have provided useful information for the conduct of future trials, including (1) successful epidemiologic studies with estimates of incidence of disease, (2) studies in different target populations, (3) development of trial endpoints for adults and children, (4) incorporation of immunoassays in human trials, and (5) experience working with regulatory authorities in endemic countries. These valuable experiences have laid the groundwork for future human studies and for raising new scientific and operational questions that can be

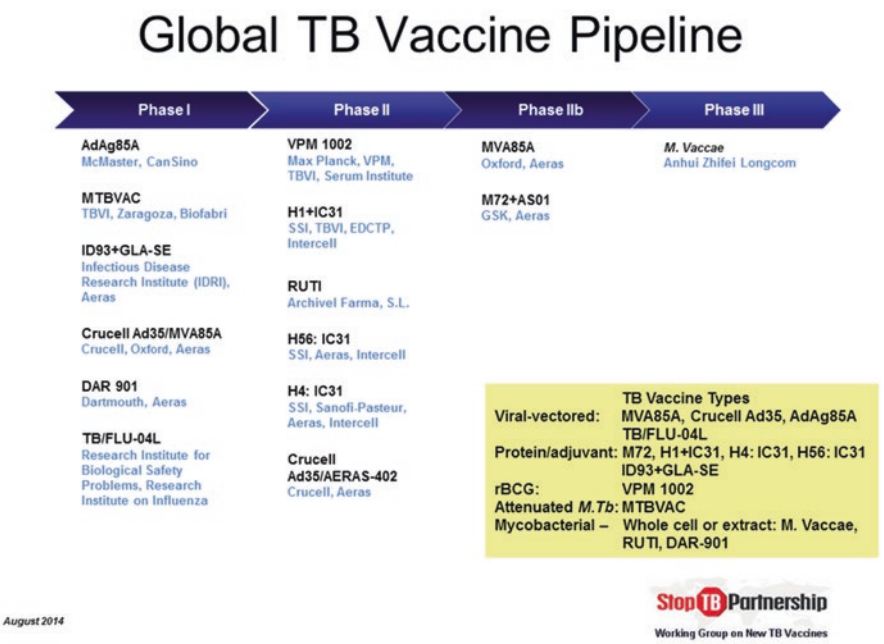

Fig. 27.1 Schematic showing TB vaccine candidates that are currently in clinical trials. Source: Stop TB Partnership Working Group on New TB Vaccines [http://www.aeras.org/pages/global-portfolio] (References for vaccines in clinical trials: *AdAg85A*: Xing et al. (2009); *Crucell Ad35/AERAS-402*: Abel et al. (2010); *Crucell Ad35/MVA85A*: Abel et al. (2010); Tameris et al. (2013); *DAR 901*: von Reyn et al. (2010); *ID93/GLA SE*: Bertholet et al. (2010); *H1 + IC31*: van Dissel et al. (2010); *H4:IC31*: Dietrich et al. (2005); *H56*: *IC31*: Aagaard et al. (2011); *M. vaccae*: von Reyn et al. (2010); Ma et al. (2011); *M72 + AS01*: Leroux-Roels et al. (2010); *MTBVAC*: Verreck et al. (2009); *MVA85A*: Hawkridge et al. (2008); Tameris et al. (2013); *RUTI*: Vilaplana et al. (2010); *TB/Flu-04L*: Stukova et al. (2006); *VPM(1002)*: Grode et al. (2005))

addressed by research. There is a need, however, for clinical studies of new TB vaccines in high-burden countries such as China and India, which may have unique epidemiological patterns of TB.

27.3 Next Generation TB Vaccines

Many challenges are faced by those investigators interested in TB vaccine research. As discussed, over the past decade, a driving force in the field has been the identification and development of the next generation of TB vaccines. Many gaps in our understanding of the disease of TB and the role of the natural human immune response following infection and colonization have become apparent. Research challenges include (1) the lack of a rational approach for identifying the best *Mtb* antigens for a vaccine; (2) animal models which give irregular results and do not

necessarily predict vaccine effects in humans; (3) the lack of knowledge of the natural human immune response which follows *Mtb* infection and prevents progression to TB disease; (4) the inability to identify an immune response in humans or animals that correlates with vaccine protection; (5) the failure of the natural immune response to prevent latent TB infection from reactivating to produce TB disease; and (6) the unknown role of immunopathology in causing TB disease and how this may be prevented during vaccination. Recently, Gagneux and Brennan (2010) have shown that six phenotypically and genotypically different *Mtb* strains are circulating worldwide. This and more recent evidence that the strains contain conserved T cell epitopes for certain vaccine antigens (Comas et al. 2010) indicate that much more effort is needed to test vaccines against endemic clinical isolates. It is clear that more intensive research in all these areas is required and new ideas are much needed to address these challenges.

Investigations in antigen discovery have focused on the early responses to infection associated with latency, hypoxic response, and virulence phenotypes (Kaufmann 2010). In the past 10 years, the selection of these antigens has been for the most part driven by the identification of antigens that elicit interferon gamma responses in either acutely or latently infected TB patients. These efforts led to the creation of a ranked list of *Mtb* T cell immunogens based on the frequency of responses among donor samples. Independent samples generated by different groups could then be cross-referenced for a final antigen selection (Zvi et al. 2008). In a variation of this approach, scientists at the Infectious Diseases Research Institute in Seattle used a bioinformatics approach followed by gating on human T cell responses in latently infected individuals, but then followed by mouse protection studies (Bertholet et al. 2008). By rank ordering on the mouse protection, a very different set of candidate antigens was assembled. This work resulted in the selection of antigens for their most recent clinical vaccine candidate, ID93 (Bertholet et al. 2010). To date, there are candidates that express early antigens, latency antigens, or PE-PPE proteins, but there are no human efficacy data to select among these candidates.

From animal and some natural history studies, the field has produced data that CD4-related interferon gamma production may be a correlate of risk for disease development, but that vaccine-induced production, as measured by present methods, is not clearly related to protection. However, in studies conducted in Cape Town, South Africa, significant differences between active TB cases and uninfected controls were associated with differential upregulation in myeloid and proinflammatory genes. A 10-gene signature differentiated between these cases and controls in a confirmatory cohort with 80 % accuracy (W. Hanekom, personal communication 2014). In studies conducted by Berry et al. (2010), gene expression patterns could be correlated with risk for TB disease progression. Of note, these signatures also correlated with the extent of radiographic involvement in both active and latent cases. This evolution of understanding correlates using gene expression signatures to enlighten the path forward has started to gain wider acceptance in the vaccine field (Pulendran et al. 2010).

Of possibly even greater significance, work from Comas et al. (2010) has drawn into question whether the conserved antigens that elicit T cell responses are actually

hyperconserved and may lead to the pathology that is required to allow for TB persistence. That is, it appears that the organism has preferentially limited the ability of T cell epitopes to mutate, in direct contradiction to what would be expected from immune selection theories. These investigators question whether some of the immune responses elicited by TB are actually orchestrated by the organism to facilitate its own survival and transmission. Clearly, a correlate of protection would greatly facilitate a new round of antigen discovery and selection.

To date, little work has been carried out to carefully classify all of the nonprotein cell wall components of TB. Although studies with lipoarabinomannan (LAM) conjugates have been published, ongoing work on the lipidome of TB by groups at Harvard Medical School, CNRS in Toulouse, and elsewhere, will hopefully lead to candidates that may drive protection through either antibody responses or through nonclassical cellular pathways (Behar et al. 2011; Layre et al. 2011).

The role of antibodies in protection against TB disease has been mostly dismissed by experts based on experimental evidence obtained many years ago, but this dismissal has been challenged by Glatman-Freedman and Casadevall (1998). It is possible that antibody response could change the overall bacterial burden and lower the risk to progressive disease or could even opsonize *Mtb* in infected subjects and lower their risk for transmitting it to others. It is also well known in the field that many effective TB vaccines in animal models are associated with the influx of a large B cell population (as are some pathogenic vaccine responses), and TB disease is enhanced in B cell Knock Out (KO) mice (Bosio et al. 2000). Yet, we know little about how these B cells are regulating the immune response or what subsets of B cells may be modifying TB immune functions.

Multiple approaches are presently being used in the arena of recombinant BCGs. These include strains that incorporate molecules that allow for endosomal escape and increase class I cross-presentation, the overexpression of TB antigens (some encoded and some not encoded by BCG), and the deletion of genes that may allow for immune escape. The latter include antiapoptotic factors, pH varying genes, autophagy genes, proteins that modify interferon sensing pathways, and even genes that modify cell wall components that may be involved in immune modulation (Barker et al. 2009; Grode et al. 2005; Kaufmann 2010).

Another area of intense interest is related to our understanding of the local adaptive or innate immune responses in the lung and to the study and modification of these through vaccination. A reassessment of mucosal delivery has begun, as past delivery of BCG by both oral and pulmonary routes has been promising (Hoft et al. 2000; Xing et al. 2009). Using a simultaneous immunization strategy, the group of Beverley et al. have shown that the effects of mucosal and parenteral delivery can be additive and result in bacterial burden reductions significantly greater than BCG alone (Beverley et al. 2013). Similar experiments have been performed using the MVA85A construct that is already in advanced human clinical trials (McShane and Hill 2005).

There are many other variables which may be critical in developing effective TB vaccines. They include an understanding of the role of exposure to nontuberculous mycobacteria (NTM), the role of vitamin D, the actual role of protective host genotypes, and the role of mycobacterial genotypes and their interaction with any of

these factors (Bartley 2010). All of these have been shown to modify the risk of disease after infection. The association of disease with periods of decreased sunlight has provoked interest in the use of vitamin D to modify TB vaccine responses. Recent data from Aeras' epidemiology studies, and similar findings from others, have shown that the use of Mycobacterial Growth Indicator Tube (MGIT) technology for liquid culture of sputum or gastric specimens from symptomatic children or adolescents with TB results in a 10–100:1 ratio of NTM isolated for every *Mtb* in a positive culture. How these endemic colonizations or infections with NTM result in modification of the host immune response to *Mtb* infection or vaccination is not clearly understood.

27.4 Access and Introduction of New TB Vaccines

As is the case for introducing new TB diagnostics and drugs (Ramsay et al. 2010; Wells et al. 2010), many factors may influence decisions to introduce new TB vaccines, replace current BCG, or boost BCG in order to provide better and more lasting protection against TB disease. Current global BCG practice is well documented in the BCG World Atlas (Zwerling et al. 2011) which reports that across countries which follow the WHO recommendation to vaccinate all infants, there is commonly variation in BCG strains used, vaccination policy, and program administration. WHO formal recommendations are likely to require evidence not only of safety and efficacy but also of public health benefit and cost-effectiveness as described for new TB diagnostics and drugs (Ramsay et al. 2010; Wells et al. 2010). A 2010 market research study of driver and barriers to the introduction of new TB vaccines revealed a wide spectrum of perspectives, many positive and some cautionary, of decision makers and stakeholders in eight high-burden countries in which interviews were conducted (Barker et al. 2011). For example, there is widespread interest in developing a vaccine for priming or boosting BCG or replacing BCG with a better TB vaccine; however, demonstration of efficacy, safety, and public health effectiveness in the population in target countries would be important for adoption and rapid uptake. As development of all three main categories of new tools for TB control advances, as well as other measures such as better infection control practices, it will be important to examine synergies in decisions to adopt and promote the best combination of new tools and practices for public health benefits in the future.

27.5 Summary

Although much progress has been made over the past decade in developing and testing new TB vaccine candidates, many questions remain about the potential effectiveness of the vaccines in human populations struggling with various manifestations of TB. More research in areas critical for vaccine development is needed while we

await the results of the first phase IIb clinical trials. Paramount among outstanding issues is the identification of a correlate of immunity for protection against TB and the development of associated assays that can be used in clinical trials that mimic vaccine effectiveness. A global effort is required to both develop and introduce new safe and effective TB vaccines.

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Part IV

Chapter 28
Global Tuberculosis Surveillance

Wei Chen, Yinyin Xia, and Fei Huang

28.1 Introduction

Tuberculosis (TB) surveillance is fundamental to modern TB prevention and control and is an important source of data for prevalence surveys and response measures. Surveillance involves the collection, analysis, and interpretation of information on TB epidemics and the influencing factors on the basis of a sound organizational structure, as well as the distribution of such information to relevant departments to inform the development of public health interventions, strategies, and measures and the evaluation of their effectiveness (Shimao 1983).

Surveillance data mainly come from registers, forms, and statistics produced by TB dispensaries according to surveillance requirements. Meaningful analysis depends on reliable epidemiological data. Additional special prevalence surveys may be conducted for particular purposes.

The modern TB surveillance concept originated in the 1950s. The United States defined standards for its national TB case reporting system, and in 1953 published the first US Annual Tuberculosis Report. Subsequently, Denmark improved the TB central registration system to include secondary registration at clinics and national centers, as well as performing basic statistical functions based on case registration and reporting, and developing national response policies based on analysis and evaluation results (Horwitz 1962). Later, some countries in Europe, such as Norway and the Netherlands, established TB central registration systems in succession. In 1965, the World Health Organization (WHO), the International Union Against Tuberculosis and Lung Disease (The Union), the Netherlands, the former Czechoslovakia, Norway, and Canada set up the Tuberculosis Surveillance Research Unit (TSRU) in

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The Hague, the Netherlands. TSRU is an international organization conducting worldwide TB epidemiological research, primarily on basic theories of TB surveillance, dynamics of TB epidemics, and effectiveness evaluation of response measures. Currently, more than 13 countries have participated in TSRU (Rouillon 1978, 1998; Bleiker 1978). Initially, paper reports were produced for surveillance results. In the late 1980s, many developed countries started to use computers to collect, store, and analyze TB surveillance data. This significantly improved the efficiency of TB surveillance. In the twenty-first century, many developed countries and developing countries have networked electronic management for TB surveillance data, which improves the timeliness of TB surveillance and provides real-time monitoring for TB prevention and control.

28.2 Routine TB Surveillance and Mortality Surveillance

The main model of TB surveillance is passive surveillance: hospitals, physicians, and laboratories (local medical institutions) routinely report surveillance data to county and state health departments who passively receive it. In contrast, active surveillance means that state or federal health departments ask local medical institutions to conduct special surveys for specific purposes and/or ask them to collect data in strict accordance with relevant stipulations. The data quality of active surveillance is better than that of passive surveillance.

The scope of TB surveillance mainly includes collecting TB epidemiological data and response data systematically through sound central registration and reporting, analyzing the trends and dynamics of TB epidemics, evaluating the effectiveness of TB response measures, improving TB response strategies based on surveillance evaluation results, and predicting the trends of a TB epidemic (Bloha 1974; Styblo 1977; Styblo and Rouillon 1981). Surveillance can be divided into TB epidemic surveillance and TB response surveillance. The status of a TB epidemic can be understood through routine surveillance, prevalence surveys, typical surveys, operations research, and surveillance sites. TB response measures and strategies can be evaluated through routine surveillance reports, periodic reports, monitoring missions and surveys (Styblo 1984; Qian 1985).

28.2.1 Routine TB Surveillance

TB response surveillance mainly covers DOTS expansion, case detection, patient treatment and management, laboratory service systems, drug supply systems, and also training and health education. TB epidemic surveillance mainly covers TB infection rate, incidence, prevalence, and mortality and may particularly target special groups such as TB/HIV co-infected patients, multidrug-resistant (MDR) pulmonary tuberculosis (PTB) patients, incarcerated inmates, and migrants.

28.2.1.1 Scope of Surveillance

Currently, information collected by the WHO through the TB Control Program covers patient data including onset, follow-up, treatment, management, and outcome. Additional data sources include quarterly and annual reports from the Register of Initial Patients, the Register of TB Patients, and the Register of TB Mycobacteriology Laboratories. Additional information pertaining to programs is also collected, including: funding, drug management, equipment, reagents, agencies, and staff. Since 1997, the WHO has published an annual global report based on information from the TB Control Program. This report details the global TB epidemic, progress in TB response, planning, financial management, research and development, existing challenges, and future program goals.

28.2.1.2 Surveillance Data Collection Methods

According to the types of reporting data, TB surveillance data can be submitted as case data or summary data. Case reports come from local medical institutions, record data from individual cases, and can be used to produce statistical forms. Summary reports are already processed by local medical institutions and do not include case information.

TB surveillance reports can be submitted in paper form, electronically, or online. Paper reports are printed and submitted to state or federal health departments via post or fax. It takes considerable time to summarize and analyze data reported on paper. Electronic reports are transferred to state or federal health departments via email or other network interfaces. This reporting method is fast and allows for speedier data processing. Online reports are directly entered online in real time. Entered data can be immediately browsed by state or federal health departments and easily summarized and analyzed.

28.2.1.3 Analysis and Use of Surveillance Data

Regular or irregular analysis of TB surveillance data can be conducted to produce analysis and summary reports to monitor and evaluate the progress and effectiveness of program implementation and improve the quality of TB response.

Routine surveillance data can be evaluated in terms of data sources, quality control, results, analysis, and discussions and recommendations.

Data Quality

To ensure data quality, administrators focus on the timeliness, integrity, and accuracy of the reports. TB surveillance data should be entered in a timely fashion according to relevant requirements. TB surveillance data should be complete

without omissions and include patient records, follow-up information, and forms. Entered TB surveillance data should be consistent with original data. On-site verification is needed to confirm accuracy and consistency between TB surveillance data and original forms (e.g., registers and paper reports).

Results and Analysis

Surveillance results are analyzed from such perspectives as case detection, treatment, and management and program information.

Case detection data are used to describe the dynamics and trends of PTB epidemic through the distribution of time, location and group, the registration of different types of PTB cases in diverse durations and locations, and other impact indicators. Diagrams (including maps) can also be used to illustrate the characteristics and trends of geographical, time, and population distribution of PTB incidences or registration rates. These diagrams help to identify the obvious region, time, and population, and analyze whether there are clusters of cases and other abnormal phenomena and define key target groups.

Treatment and management data are mainly used to analyze patient follow-up and treatment outcomes. Outcome data includes the number of smear-positive PTB patients with negative conversion after 2-month and 3-month treatment, negative conversion rates, and the cure rate, mortality rate, and failure rate of different types of registered PTB patients. Treatment outcome data will be compared with data in previous years to identify areas with abnormal results and conduct further analysis of influencing factors.

Program management data are mainly used to analyze the implementation of program activities, such as funds, human resources, agencies, equipment, drugs, monitoring, health education, and training.

Discussions and Recommendations

Any issues identified during the data analysis, including evaluation of data quality, surveillance results, and/or special challenges should be addressed. For all identified issues, specific recommendations should be put forward.

28.2.1.4 Cases

China

Routine TB surveillance in China covers annual reports, quarterly reports, monthly reports, and web-based electronic case surveillance systems. Specifically, annual reports were started in 1981. All provinces submitted annual reports. The first

annual report only covered the number of PTB patients of different types detected and registered in each province. Later, new elements were added, including the treatment outcome of registered PTB patients, age groups of new smear-positive PTB patients, funds in TB response, composition of human resources, and models of TB response.

Quarterly reports were used for the World Bank's Health V Project in 13 provinces. In 2002, quarterly reports were gradually expanded throughout the country.

In 2004, monthly reports were used across the country and mainly covered the referral and tracing of PTB patients/suspected PTB patients reported by non-TB dispensaries.

By 2005, all TB dispensaries in China started to use and submit quarterly reports. These reports were summarized and verified by provincial TB dispensaries. Provincial summary reports were submitted to the National Center for TB Control and Prevention (NCTB). The scope of quarterly reports covered the detection and registration of PTB patients, sputum negative conversion, and treatment outcome.

In 2005, China started to use the TB information management system. This system is an Internet-based electronic surveillance system focusing on individual patients. TB dispensaries at all levels entered data on individual PTB patients into the system, and the system would automatically summarize the data and produce relevant reports. Real-time data exchange was achieved between the TB information management system and the national infectious disease reporting system, ensuring the consistency of data between these two systems.

The United Kingdom

In 1913, all types of TB cases were defined as a notifiable infectious disease by law. All medical practitioners are required to report TB cases to officials (generally the local Consultant in Communicable Disease Control, CCDC). By 1965, TB was only reported as an infectious disease in the Notifications of Infectious Diseases system (NOIDs).

In 1998, Enhanced Tuberculosis Surveillance (ETS) was used to collect demographic, clinical, and laboratory data of all TB patients reported to the Health Protection Agency since previous prevalence survey indicated high TB incidence and NOIDs could only collect limited data. In 2002, ETS added treatment outcomes of patients.

In 2008/2009, ETS started to report TB cases via Internet, enabling real-time case reporting and access to information on individual patients. In addition to patient information collected by ETS, the online reporting system collected information on the dwelling status of patients and risk factors such as incarceration and drug use. The new ETS system can be linked to the UK TB surveillance network (Health Protection Agency 2009).

The United States

Official case reporting began in 1953 and TB reporting criteria were revised in 1975. By the end of 2010, the Tuberculosis Information Management System (TIMS) was used to collect information on TB patients (Centers for Disease Control and Prevention (CDC) 2010). In 2010, the National Electronic Disease Surveillance System (NEDSS) was launched to streamline case reporting of TB and other diseases.

Japan

In 1975, a computerized surveillance system was established in Okinawa Island to monitor TB infection rate among children. In 1981, a similar surveillance system was launched in Aichi County and Shizuoka County, and the national infectious disease surveillance system was expanded across the country. In 1987, Japan established the first national computerized TB and infectious disease surveillance system. The system was revised in 1992, 1998, and in 2007. Users of the public health center can report data to the national database in real time, but the national database only collects and evaluates data related to the TB Control Program. Other data are stored in local databases (Ohmori et al. 2007). All TB patients should be reported within 2 days after the diagnosis (Calvarese 1999).

South Korea

In 2000, South Korea started to use the Internet-based Korean TB Surveillance System (KTBS), focusing on the registration (onset) and treatment outcome of TB patients to provide evidence for public health policy-makers to develop specific policies, laws, and regulations.

The newly revised Korea Action Program for Infectious Diseases and Korea Action Program for Tuberculosis stipulates that doctors should report TB cases to local healthcare centers within 7 days after confirmatory diagnosis. TB cases could be reported through logging on the web-based direct reporting system or faxing TB registration cards to local healthcare centers for online reporting (Korea Center for Disease Control and Prevention 2011).

Brazil

Brazil's Ministry of Health developed the Information System for Notifiable Diseases (SINAN) in 1993. This registration and reporting system for infectious diseases includes general TB cases. Health facilities at all levels fill in paper reporting cards for detected TB patients and submit these cards to the municipal level on a monthly basis. The municipal level enters the information into SINAN, and provincial and national levels can conduct online query and analysis of data (Braga 2007).

In 2005, an additional web-based TB management information system, SITE-DRTB, was added for special cases including drug-resistant (DR) TB, severe cases, HIV-positive patients, and homeless patients. This system was based on the e-TB Manager tool developed by USAID and the non-governmental organization Management Sciences for Health (MSH). This system provides a surveillance platform integrating patient management, drug management, and epidemic surveillance. It includes four modules: case information, drug management, planning management, and system authority management (MSH 2005). SITE-DRTB was implemented countrywide by 2007 and formally used in 162 public DR-TB treatment centers by 2011.

28.2.2 TB Mortality Surveillance

TB is one of the top 15 causes of death for human beings and should be defined as a priority in public health and disease control. One of the Millennium Development Goals (MDGs) is to halve TB mortality by 2015 compared with the levels in 1990 (Dye et al. 2006). To monitor TB mortality and disease burden, all countries have increased funding input in TB control and made great efforts to improve the TB vital registration system. In 1970, 65 countries submitted vital data to the WHO, and this increased to 90 in 1999 and 115 countries in 2003. Nevertheless, the vital registration system varied significantly in different countries. In 2003, analysis results for global vital registration systems indicated that 100 % of countries in Europe had vital registration data, but less than 10 % of countries in Africa had such data. Among the 115 countries submitting vital data to WHO, only 64 countries reported complete vital surveillance data, mainly in Europe, America, and the Pacific Region (Mathers et al. 2005).

Three methods can be used to evaluate TB vital surveillance (Klaudt 1994): (1) International Classification of Diseases (ICD) coding can measure TB mortality through the national vital registration (VR) system; (2) The sample vital registration (SVR) system and verbal autopsy (VA) are combined to monitor TB mortality; (3) TB deaths are recorded through DOTS treatment cohorts and TB mortality is indirectly estimated through case fatality rates (CFRs).

The vital registration system generally collects vital information in a continuous way after standardization at the national level, directly evaluates the mortality, and is very useful for looking at any mortality changes. It is the most direct and reliable method to evaluate TB mortality. Indicators of the vital registration system include life expectancy and mortality data that is gender specific, disease specific, and age specific (including infant mortality). As for diagnosis, the order of reliability is: autopsy, pathology, operation, clinical examinations, physical/chemical tests, and presumptive diagnosis after death. Countries that have used the vital registration system to estimate TB mortality should evaluate the effectiveness and accuracy of system surveillance data on a regular basis, in a bid to reduce the proportion of TB cases without treatment outcomes (Rao et al. 2005).

Verbal autopsy (VA) is an indirect method of ascertaining cause of death from information about symptoms and signs obtained from bereaved relatives (who provide care for patients before their deaths and/or can clearly describe the illness of patients) (Rao et al. 2005; Byass et al. 2003). Over the past years, the VA instrument has been extensively applied in countries/regions with poor performance in census and vital registration systems and/or where significant numbers of the population die outside of the hospital system. It has become a main tool to estimate the Cause Specific Mortality Fractions (CSMFs) among a specific group. In developed countries, the verbal autopsy scale has been widely used to verify potential causes of death and evaluate the effectiveness and integrity of the vital registration system (Korenromp et al. 2009; Chandramohan et al. 1998; see Table 28.1).

The VA instrument can also be based on the sampling vital registration system. Some countries that have not set up population sampling sites attempt to use VAs to evaluate potential causes of death and the distribution of such causes based on death data from hospitals (Moorman and Edginton 1999; Murray et al. 2007). VA tools have different effects in evaluating CSMF among different groups. Studies indicate good consistency in presumptive causes of death and diagnosis made by hospitals among children and women, so the VA instrument has been widely used to judge causes of death among these two groups. In developed countries and cities, many patients die in hospitals, so the VA instrument has high sensitivity and specificity. Data on the distribution of death causes from hospitals can be corrected to evaluate such distribution at the national level. Note that in areas with low social and economic status and poor accessibility of health services, death data from hospitals are not recommended for the evaluation of TB mortality.

Strictly, case fatality rate (CFRs) is the cause specific mortality fraction (CSMF) in a specified period of time (Beaglehole et al. 1993). For convenient calculation, CFR is often defined as the mortality of TB treatment cohorts. For countries without vital system data, WHO uses TB incidence and CFR to estimate the total TB mortality (WHO 2009b), but it is difficult to estimate CFRs by age and gender (Crofts et al. 2007).

The global TB mortality is on the decline compared with the level in 1990 (Fig. 28.1). Nevertheless, the TB mortality in African and Europe (mainly Eastern Europe) is on the rise since 1990. Although this situation was improved after 2000 (in Europe) and 2005 (in Africa), TB mortality is still higher than that of 1990 in Africa and close to that in 1990 in Europe. This makes it very difficult to achieve the goal of halving the TB mortality rate (compared to 1990) worldwide by 2015 (WHO 2009a).

In China, population-specific mortality reports were available in various provinces from 1917 to 1933, but there were no national TB mortality data. After 1949, TB mortality reported in some large cities and a few provinces was very high (Wang 2005), ranging from 164/100,000 to 250/100,000 (see Table 28.2).

In 1954, China established the national birth and vital registration systems, and the National Bureau of Statistics started to publish mortality statistics. From 1954 to 1982, the total crude mortality published every year was the mortality reported by the household registration system.

Since the 1980s, a routine registration system was put into operation which covers more target groups. Since 1990s, vital registration covered a stable number of target

Table 28.1 TB vital registration system and effectiveness

Region	Reference	Source of data	Time	Coverage	TB CSMF %	Verbal autopsy scale	Effectiveness of vital registration system				Data quality
							Sensitivity	Specificity	PPV	Consistency	
Chennai, India	Gajalakshmi et al. (2002)	VA	1995–1997	100 %	–	–	54	96.7	74	0.87	
Chapas, Mexico	Nájera-Ortiz et al. (2008)	VA	2002	100 %	–	✓	79	–	–	0.61	High
		NTPs									
New York, USA	Washko and Frieden (1996)	VR	1992	100 %	–	–	34	–	60	–	High
		NTPs									
Rural areas, China	Wang et al. (2007)	DSP	2002	1 %	20.1 CMFRs	✓	30	88	44	0.35	–
Urban areas, China	Rao et al. (2007)	VA	2002	6 cities		✓	87	99.7	87	0.994	–
England and Wales	Crofts et al. (2007)	NHS	2001–2002	100 %	4.8 CFRs	–	45	–	–	–	Good
		ONS									
		NTPs									
Tanzania	Setel et al. (2006)	DSS	2000–2003	3 districts	–	✓	0.19	0.98	0.12		Poor
Norway	Heldal et al. (1996)	NTPs statistics	1977–1989	100 %	–	–	67	99.97	72	0.999	–
Queensland, Australia	Walpola et al. (2003)	NTPs	1989–1998	100 %	8.7 CFRs	–	–	–	–	–	–
Delhi, India	Saha et al. (2007)	NTPs	1994–2004	–	24.8 CMFRs	✓	–	–	–	–	–
Taiwan	Wu et al. (2008)	VR	2001–2005	–	–	✓	84		83	0.71	–
Thailand	Tangcharoensathien et al. (2006)	VR	2004	96 %	2.3	✓	–	–	–	–	Poor
Cape Town, South Africa	Bradshaw et al. (2006)	VA	1999	88 %	5.9	✓				0.73	Poor

CFR case fatality rate, *DSP* disease surveillance point, *DSS* dsease surveillance system, *NHS* national health service, *NTP* national tuberculosis program, *ONS* office for national statistics, *VA* verbal autopsy, *VR* vital registration

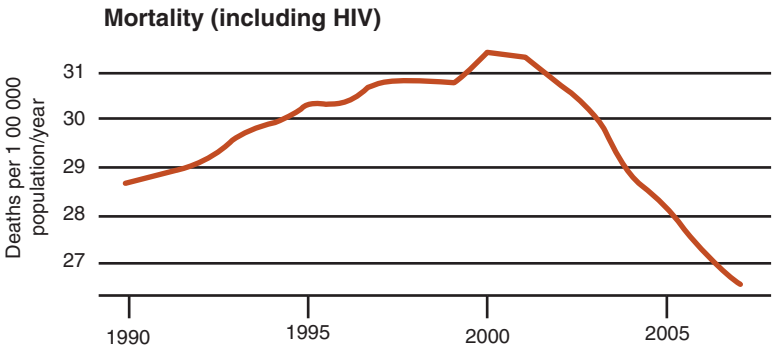

Fig. 28.1 Trend of global TB mortality from 1990 to 2007 (including HIV-positive TB patients)

Table 28.2 TB mortality in some areas in China circa 1949 (Wang 2005)

Province/city	Year	TB mortality (per 100,000)	Province/city	Year	TB mortality (per 100,000)
Beijing	1949	230	Shanghai	1951	209
Tianjin	1949	164	Guangzhou	1951	225
Liaoning	1950	250	Changchun	1952	171

Table 28.3 Three prevalence surveys on mortality (MOH 1988, 1992, 2003)

	Mortality (per 100,000)		
Category	1983/1984	1989	1999
TB	35.0	20.4	9.8
PTB	31.0	19.1	8.8

groups, but mainly covered urban areas and rural areas in eastern China. The surveillance results were not representative for the whole country. Currently, the main vital registration systems in China include: the Ministry of Health (MOH)'s Vital Registration (VR) System, the Chinese Center for Disease Control and Prevention's Disease Surveillance Point (DSP) System, a web-based direct death reporting system for health facilities at county and higher levels, and a web-based TB reporting system. The DSP system is the leading tool for vital evaluation (Yang 2005).

Retrospective surveys on TB mortality were conducted based on the findings of prevalence surveys, respectively, in 1983/1984, 1989, and 1999 (MOH 1988, 1992, 2003; see Table 28.3).

WHO mainly uses TB prevalence and TB incidence to estimate TB mortality in China. Figure 28.2 illustrates the change of TB mortality from 1990 to 2007. According to a report from the WHO in 2009, about 200,000 people died of TB in China in 2007. This mortality rate of 15/100,000 is an improvement over the 25/100,000 previously reported in 1990 (WHO 2009a).

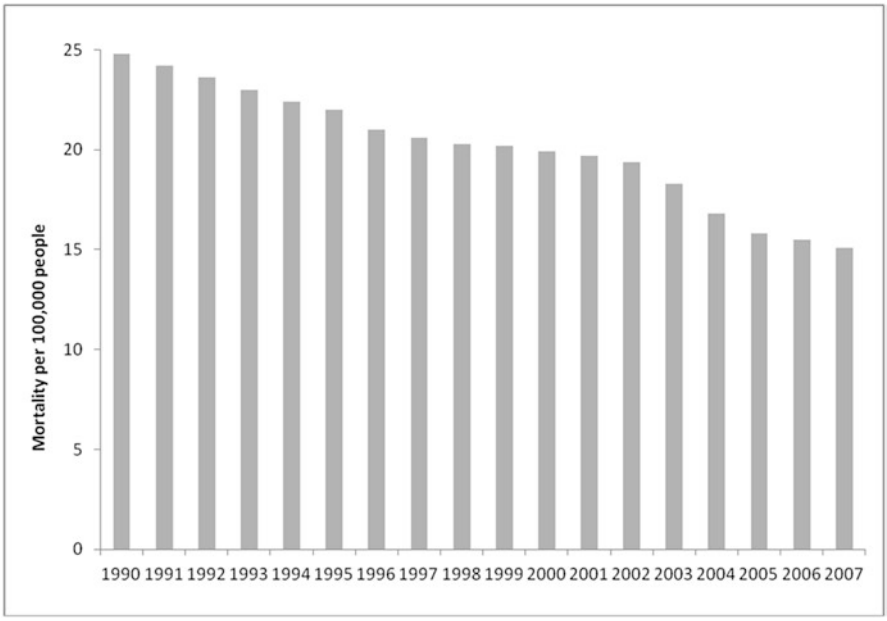

Fig. 28.2 Change of TB mortality in China from 1990 to 2007 (WHO 2009a)

28.3 TB Prevalence Survey

A TB prevalence survey is a population-based cross-sectional survey and uses standardized diagnostics to detect patients, so as to reflect the prevalence among a specific group in a particular area during a particular period of time. It can produce accurate prevalence, evaluate disease burden, assess case detection, and demonstrate the dynamics of a TB epidemic. Nevertheless, a representative national prevalence survey requires a large sample size and huge human and material resources, and also faces difficulties in organization and implementation. Therefore, prevalence surveys have been replaced by TB surveillance data in some developed countries with low prevalence and sound case detection and registration. In countries with high TB burden, especially where case detection can not reflect TB prevalence, prevalence surveys are still necessary (Styblo 1991; WHO 2009c, 2011).

28.3.1 Global TB Prevalence Surveys

Since the 1950s, Japan, South Korea, and other countries conducted several prevalence surveys in succession in order to look at domestic epidemics and provide evidence for response strategies (see Table 28.4). After organizing several

Table 28.4 Previous TB prevalence surveys

Country (reference)	Number of surveys	Years	Last morbidity survey			
			Number of survey subjects	Survey methods	Survey findings	Conclusions and features
Japan (Shimao 2009)	5	1953 1958 1963 1968 1973	45,682 people	X-ray (radiography) performed for previous patients and close contacts	Morbidity: 1000/100,000 for active TB and 60/100,000 for smear-positive TB	Prevalence surveys in 1953, 1958, and 1963, respectively, selected one-third subjects to conduct an addition survey in the subsequent year to identify TB incidence. Since 1973, surveillance data replaced prevalence surveys due to the decline of TB morbidity and the need for a large sample size
South Korea (Hong et al. 1998)	7	1965 1970 1975 1980 1985 1990 1995	64,713 people	Multi-stage stratified cluster sampling method was used to select 203 survey sites. Tuberculin skin testing and BCG scar examination were performed for subjects under 30 years. X-ray was performed for subjects over 5 years. Three sputum specimens were collected from each suspect to perform smear, culture, and DST	The proportion of subjects under 30 years and with BCG scar increased from 86.0 % in 1990 to 91.8 % in 1995. The prevalence also decreased among subjects without BCG inoculation. Morbidity was 93/100,000 for smear-positive TB, on a decline in comparison with previous prevalence surveys. The total drug resistance rate was 9.9 %	The vaccination rate was very high. TB prevalence among children declined rapidly. The morbidity declined for active TB, smear-positive TB, and *Mycobacterium tuberculosis*-positive TB, with the fastest decline for smear-positive TB. The proportion of drug resistance cases also declined. The seven prevalence surveys indicated a continuous decline of TB morbidity, especially in 1980s. However, great efforts should be made to strengthen TB response among people of several age groups
Vietnam (Hoa et al. 2010)	1	2006–2007	94,179 children ≥ 15 years and adults	Multi-stage stratified (i.e., urban areas, rural areas, and remote areas) cluster sampling method was used to select 70 survey sites. History taking and X-ray films were used to identify suspects. Three sputum specimens and X-ray film were used to give confirmatory diagnosis. During the analysis process, weighing was adopted to adjust the stratified sampling method, population growth rate, and cluster size	Morbidity: 196.8/100,000 for smear-positive TB and 307.2/100,000 for *M. tuberculosis*-positive TB. The morbidity for smear-positive TB among males was 5.1 times of that among females. The morbidity for *M. tuberculosis*-positive TB among males was 4.6 times of that among females	The total TB morbidity was 1.6 times of the estimate made by WHO. The disease burden was high. Only 53 % of patients had the symptom of cough. The National TB Control Program missed or delayed the detection of these asymptomatic patients. Great efforts should be made to strengthen case detection among males

China (MOH 2000)	5	1979 1984–1985 1990 2000 2010	252,940 children ≥ 15 years and adults	Multi-stage stratified (urban and rural area) cluster sampling method was used to select 176 survey sites. Symptom survey and X-ray were used to identify suspects. Three sputum specimens were collected from each suspect to perform smear, culture, and DST	Morbidity: 66/100,000 for smear-positive TB and 119/100,000 for *M. tuberculosis*-positive TB, significantly lower than those in the previous prevalence survey. The morbidity for active PTB decreased slowly	The proportion of smear-positive TB cases among active TB cases, the proportion of *M. tuberculosis*-positive cases among active TB cases and the proportion of symptomatic patients were all low, reflecting new disease characteristics. Case detection should be strengthened for older and asymptomatic patients. Geographical difference in TB morbidity indicated the need to boost TB response in central and western China, rural areas, and ethnic minority areas
Bangladesh (Child Health Unit 2010)	3	1964–1966 1987–1988 2007–2009	52,098 children ≥ 15 years and adults	Multi-stage cluster sampling method to select 20 urban survey sites and 20 rural survey sites. Two sputum specimens were collected from each subject to perform smear examination. One additional sputum specimen from each subject with positive smear result and X-ray were used to give confirmatory diagnosis	Morbidity: 79.4/100,000 for smear-positive TB, significantly lower than that in the previous prevalence survey. The morbidity among males was three times of that among females	Special attention should be paid to older people, rural residents, and people with low social and economic status. The first prevalence survey since the implementation of DOTS in 1993 showed the decline of smear-positive TB morbidity and achievement of the Millennium Development Goal
Eritrea (Sebhatu et al. 2007)	1	2005	38,032 people	Selected 40 villages by probability proportional to population size sampling. Two sputum specimens were collected from each subject over 15 years to perform smear examination. In villages where there were smear-positive patients, X-ray was performed for smear-negative subjects. All smear-positive patients received HIV antibody test	The crude prevalence of smear-positive TB was 83 per 100,000 individuals (totaling 19,197) aged 15 years or more. All patients had a negative HIV test result. The estimated prevalence of new smear-positive TB was 50/100,000 in the total population. This is considerably lower than the WHO provisional estimate for 2005 of 251/100,000	This survey of TB prevalence in Eritrea is the first national TB prevalence survey conducted in Africa in 45 years. The new approach tested (i.e., collecting samples from all individuals aged 15 years or more and examining the samples by fluorescence microscopy) proved to be feasible. The cost of the survey was approximately €200,000. The approach tested in this national survey in Eritrea could facilitate the performance of surveys of TB prevalence in countries where limited resources are available

BCG bacille Calmette-Guérin, *DOTS* directly observed treatment, short-course, *DST* drug sensitivity testing, *HIV* human immunodeficiency virus, *TB* tuberculosis

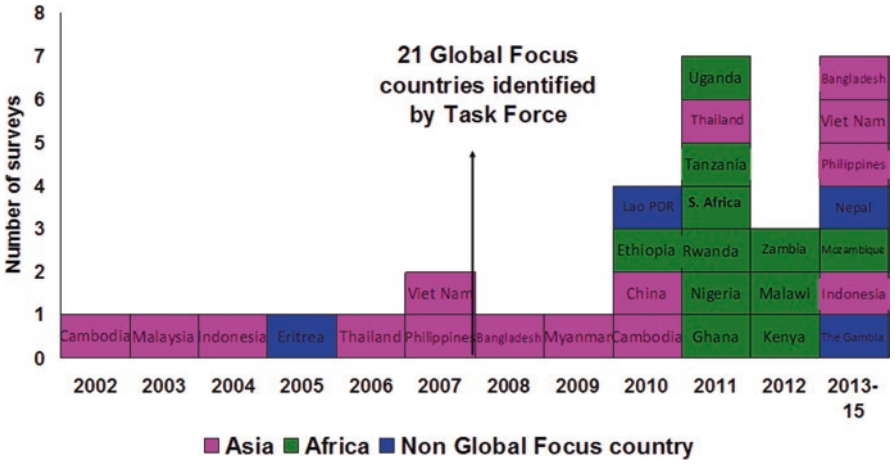

Fig. 28.3 Progress and planning of TB prevalence surveys in different countries from 2002 to 2015 (Ikushi Onozaki)

prevalence surveys, Japan and South Korea identified the rapid decline of domestic TB epidemics and started to implement routine surveillance in replacement of national prevalence surveys. Since 2000, with support of the WHO and other international organizations, more developing countries have implemented national prevalence surveys or developed prevalence survey plans (Fig. 28.3). For example, Vietnam, Philippines, and China have implemented new prevalence surveys. Vietnam found that the national prevalence was 1.6 times of the estimate made by the WHO, and this prevalence survey significantly contributed to domestic TB response. China conducted a prevalence survey in 2010, and survey findings indicated a decline in the number of infectious PTB cases, but a rise in the proportion of asymptomatic PTB patients, providing evidence for adjusting future directions of response strategies. In 2005, Eritrea organized the first national prevalence survey in Africa and found that the national prevalence was lower than the estimate made by the WHO. Survey methods in Eritrea were highly cost-efficient and could be adapted by other countries with limited resources.

28.3.2 Application of Prevalence Survey

28.3.2.1 Direct Application

The core result of prevalence survey is the geographically representative TB prevalence data, which may include the prevalence of active TB, smear-positive TB, *Mycobacterium tuberculosis*-positive TB, cavity TB, new TB patients, DR-TB patients, etc. The country's disease burden can be calculated based on the prevalence

result and the population size. The groups at high risk of TB or areas with high prevalence can be identified through the analysis of the prevalence of various subgroups surveyed. If past prevalence survey findings are available, they can be compared to understand the dynamic trend of prevalence, the high risk groups, and changes in the prevalence areas, or to assess the outcomes of TB response efforts during the interval between two surveys. These can provide important evidences for assessing the TB epidemic situations and developing targeted national TB control program.

28.3.2.2 Indirect Application

In addition to prevalence, there are two other indicators commonly used to measure the TB burden: incidence and mortality. In prevalence survey, if incidence is not included, it can be indirectly estimated based on prevalence. Six methods are commonly applied internationally for the calculation of TB incidence (WHO 2009c), including calculation directly based on surveillance data, directly through prospective study, and indirectly through annual prevalence, morbidity, case fatality rate, or case detection rate. The relatively accurate prevalence obtained from prevalence survey can be divided by the average TB disease duration in order to obtain the estimated annual TB incidence.

Subsequently, mortality can be estimated. Three methods are commonly applied to calculate the TB mortality: utilization of data from the death cause registration system, verbal autopsy study, and estimation based on incidence and case fatality rate (WHO 2009c). The incidence that is estimated based on prevalence survey can be multiplied with TB case fatality rate to obtain TB mortality.

TB patients may not be registered in the TB registration/surveillance system due to various reasons (e.g., they fail to attend clinic or receive diagnosis, or they are not reported or registered) resulting in a discrepancy between the actual number of patients and the number of registered patients. This can be reflected by the case detection rate, which can be obtained by dividing the TB annual incidence estimated according to prevalence survey by the reported TB annual incidence as per the registration system.

28.3.2.3 Adjacent Studies

A prevalence survey is generally conducted in the general population. This can generate information on the people without TB and can better reveal the general situations of TB patients, thanks to the active detection instead of the passive detection practiced by the TB surveillance/registration system. A prevalence survey usually involves a large sample size and features geographic representativeness. Therefore, countries usually carry out adjacent studies in the course of prevalence survey. Common adjacent studies are listed below.

Socioeconomic survey. Prevalence survey focuses on the prevalence. Further survey is necessary to understand the impact of social and economic conditions of

patients upon the prevalence, particularly their clinic attendance, treatment. Therefore, socioeconomic survey is often coupled with the survey on TB control program and management in order to identify the gaps in the TB response and the key factors affecting the patients' clinic attendance, detection and standardized treatment, and therefore can inform the identification of key target groups of TB response and adapt the TB control measures.

Survey of awareness. Along with prevalence survey, questionnaire survey on TB awareness can be conducted with the general population, in order to understand the awareness of TB prevention approaches, transmission routes, symptoms, treatment and prognosis, and state policies on TB control among healthy people and patients. This survey can assess the effectiveness of health education activities, and identify the key target groups and areas for health education if coupled with socioeconomic survey.

Vaccination rate survey. This survey is designed to understand the vaccination of various groups and the dynamic trend through a questionnaire on the history of BCG vaccination, BCG scar observation, etc. and assessment of the quality of vaccination to help identify the key target groups. With reference to the TB prevalence survey findings, it can also evaluate the protective effect of vaccines.

Infection rate survey. This survey is designed to estimate the rate of *M. tuberculosis* infection among the population, through tuberculin test or other tests, which is crucial for assessing the infections among the population, as well as determining the scope of vulnerable groups and the estimation of incidence. Infection rate can also be used to derive the annual infection rate, or directly generate annual infection rate if the survey is repeated within the 12 months that follow the initial survey.

Incidence survey. A repeat survey among the non-TB persons within a period of time (usually 1 year) following the prevalence survey can generate reliable incidence data. If a portion of the population is selected as the prospective follow-up cohort and prevalence survey findings are available, data on TB infections and the natural incidence history can be obtained to reveal the pattern of incidence.

Mortality survey. In countries without a robust death cause registration system, a mortality survey is a key approach to assessing the TB-related death burden. Based on prevalence survey, relatively accurate death data can be obtained by deducing the causes for deaths according to the verbal autopsy of the family members of deceased in a period of time (usually 1 year) at the survey sites.

28.4 Concluding Remarks

TB surveillance is the basis for TB prevention and control and a key source of epidemiological information and information on TB response. Surveillance data are mainly provided by the central registration systems and reporting forms created by TB dispensaries for surveillance purpose as well as special prevalence surveys. Current international practices suggest that the appropriate surveillance approach is

based on a sound routine surveillance system and may include special prevalence surveys as necessary.

In the analysis of surveillance data, important and sensitive surveillance indicators should be used. TB incidence and prevalence are the two key indicators for assessing TB epidemic. In developed countries with robust case registration systems, incidence is generally reflected by the new TB registration rate; if incidence data are obtained via special prevalence survey, huge costs may be incurred, and consistently comparable incidence data can hardly be obtained due to the constraint of single survey findings. Similarly, TB prevalence is obtained through TB prevalence surveys which have been developed in few countries due to the huge costs in human, physical, and financial resources. As the TB epidemic is gradually weakened, more costs and complexity are involved in TB prevalence survey. The optimal solution is still to estimate the prevalence and its dynamic trend by referring to the TB registration rate based on data from a sound case registration system.

To assess the causes for TB deaths, countries should select the appropriate assessment methods in consideration of the situations of the local death registration systems, preferring surveillance system data with high sensitivity and specificity. Gradually establishing quality vital registration systems, using International Classification of Diseases (ICD) codes to identify the causes for deaths, and promoting the use of verbal autopsy scale should become the next steps for the development of TB death surveillance systems in developing countries.

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Chapter 29
Factors Affecting the Incidence of Tuberculosis and Measures for Control and Prevention

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29.1 Introduction

Tuberculosis (TB) is a serious threat to global public health. TB not only reduces a patient's life expectancy, it can significantly reduce an individual's and society's quality of life. The heavy burden that it will place on healthcare resources and the resulting effect on global socioeconomic development cannot be ignored (Ministry of Health, and Disease Control Division 2006; Wei and Xiao 2009). According to World Health Organization (WHO) estimates, in 2013 there were more than 11 million TB patients around the world, with more than nine million incident cases expected each year (WHO 2014a).

TB infection is governed by a complex interaction between the host and the pathogen *M. tuberculosis*. Whether or not an individual becomes infected is due to a variety of factors, including the opportunity of exposure to pathogens, differences in pathogen virulence, hosts' behavioral factors, immune factors, genetic factors, and environmental and socioeconomic factors (Li 2004).

Although efforts spearheaded by the United Nations Millennium Development Goals to halt and reverse the incidence of TB around the world may have been successful, the incidence reduction ratio is less than 1 % annually, and the number of TB patients has increased year by year because of population growth (Lönnroth et al. 2010a). Thus, in order to take more targeted measures to strengthen the TB epidemic control and make significant reductions in the incidence of TB, we have to explore factors in addition to detection and treatment to eliminate sources of infection. This chapter focuses on the incidence of TB associated with individual and group factors and strategies for prevention and control of these factors.

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29.2 Factors Affecting the Incidence of TB

The list of known and suspected factors related to TB infection includes genetic factors, personal behavior, individual biological factors related to immunization status, history of contact, environmental factors, and socioeconomic conditions.

29.2.1 Gender

Although studies have shown that women infected with *M. tuberculosis* develop TB disease faster than men (WHO 2005a), prospective studies and registration reports have shown that men's risk of developing TB was significantly higher. India Tuberculosis Research Center carried out a 15-year follow-up study in southern India in 1968. This research documented 280,000 people in rural India and found that men have a TB relative risk of 3.0 (95 % CI: 2.7–3.2) after adjusting for age, compared to women (Radhakrishna et al. 2003). In addition, men always have higher TB registration rates than women (WHO 2005a). This phenomenon can be explained from two angles: biological/physiological and sociological. From a biological/physiological point of view, there are gender differences in immune response. Female hormones are known to activate the immune system, and the male hormone testosterone has immunosuppressive effects (Cutolo et al. 2004). From a sociological point of view, the difference can be primarily attributed to the differences in the division of labor. In China, men are more extensively involved in social activities, resulting in a greater risk of exposure (Holmes et al. 1998) and have higher rates of smoking and drinking, as well as performing most of the heavy manual labor. All of these factors increase the rate of infection after exposure and the probability of disease. Another possible reason is that due to socioeconomic and cultural factors, women seek medical treatment at a lower rate than men, thus leading to lower rates of TB diagnosis and registration (Hudelson 1996).

29.2.2 Age

There is clear evidence that the older the people are, the higher their risk for TB incidence (National Tuberculosis Institute 1974; Radhakrishna et al. 2003). The cohort studied by the India Tuberculosis Research Centre in 1968 showed that the risk of TB increased linearly with age, after adjusting for gender factors. Compared with the 0–4 age group, other age groups' adjusted RR values progressively increased from 1.7 to 10.8 (Radhakrishna et al. 2003). Possible reasons are an increase in exposure opportunity with age, a decline in immune function with age, and an increased opportunity for alcohol, smoking, and the accompanying negative life events (Meyer 2005). In addition, the overall risk of disease (and secondary infection) increases with age, which adds to the risk of TB (Vynnycky and Fine 1997).

29.2.3 Genetic Factors

As a single infection factor, TB is the disease that causes the most death. However, only one-tenth of the infected population develops active TB (Xie et al. 2003). This indicates that individual differences may be associated with susceptibility to TB. Evidence of genetic factors in the pathogenesis of TB was reported by Stead et al. (1990) in a classic epidemiological study. The study focused on a population of 25,000 tuberculin test negative individuals. The living environment and lifestyle of the cohort was very similar to a nursing home. They found that TB infection varied among races, and that a genetic predisposition to TB indeed existed in different races. A prior study on twins showed that the prevalence in identical twins is more consistent than in fraternal twins, indicating that even within the same race, genetic factors play a significant role in TB infection (Comstock 1978).

The current research on the relationship between genes and TB susceptibility is focused on two types of genes. The first type are human leukocyte antigen (HLA) genes such as HLA-DR3, HLA-DQw3, and HLA-DR4. Their relationship with TB infection has been studied in a number of ethnic groups (Bothamley et al. 1989; Goldfeld et al. 1998; Terán-Escandón et al. 1999) but the results vary (Hafez et al. 1985; Hwang et al. 1985; Hawkins et al. 1988; Khomenko et al. 1990; Brahmajothi et al. 1991; Selvaraj et al. 1996). The second type are non-HLA genes including the vitamin D receptor gene (VDR), natural resistance-associated macrophage protein l (NRAMP I) gene, mannose binding lectin (MBL) gene, nitric oxide synthase (NOS2) gene on the X chromosome, and CD40 ligand genes (Davies and Grange 2001). Relatively more is known about the genetic mechanism of the first three genes; however, in studies of the same genes, different research groups may come to different or even opposite conclusions (Bellamy et al. 1999; Wilkinson et al. 2000).

29.2.4 Factors Related to Immune Status

Many factors affect the incidence, process, and outcome of TB infection directly or indirectly through stimulation of the immune response. The immune response to TB is mediated by T-lymphocyte cells involving a variety of cytokines with both negative and positive influences (Yu 2002). But their exact function and their roles in the pathogenesis of TB remain unclear. It is known that HIV infection, malnutrition, diabetes, smoking, alcohol, and indoor air pollution (all factors associated with immune status) have an impact on TB.

29.2.4.1 HIV Infection

A large number of studies have shown that HIV infection is a clear risk factor for TB; the HIV-positive OR is 26.7 (95 % CI: 20–35) for developing TB (Lönnroth et al. 2010b). Although the incidence of TB/HIV co-infection varies among

countries and regions, the incidence of TB in the HIV/AIDS populations is always higher than in the local general population (Korenromp et al. 2003). Two case-control studies in Tanzania separately showed that HIV infection is an important factor in the increased incidence of TB over the past decade (van den Broek et al. 1993; van Cleeff and Chum 1995). In the areas where HIV prevalence reached 10 % of the country, 40 % of smear-positive TB patients were associated with HIV infection. Two other studies carried out in South Africa supported this conclusion (Corbett et al. 2000; Sonnenberg et al. 2004). Studies of special populations, including prisoners and newborns, also show that the incidence of HIV infection is a risk factor for TB (Sánchez et al. 1995; Hesseling et al. 2009). Studies at the molecular level have shown that HIV-infected individuals are more susceptible to first time TB, and HIV infection can increase the risk of TB recurrence (Ellis et al. 2002).

HIV has the ability to damage the immune system and reduce the number and function of CD4+ cells in the circulatory system. This leads to a decrease in production of the cytokines IL-2 and IFN, which severely restricts the ability of cells to respond to the *M. tuberculosis* antigens. Of particular importance is a reduction in the ability of macrophages to inhibit the growth of *M. tuberculosis*, which can lead to active TB infection (Toossi et al. 2001). Another important factor is an immune defect that leads to the formation of lesions in the body that contain TB in a dormant state. These lesions can lead to the reactivation of TB at a later time (Raja 2004).

29.2.4.2 Malnutrition

There is a relationship between TB and deficiencies in protein, calories, vitamins (A, D, C, E), and minerals (zinc and selenium). However, most of the evidence is from cross-sectional studies relying on causal inference. Some cohort studies based on the relationship of nutrition and TB consider body mass index (BMI) as an indicator of nutritional status (Cegielski and McMurray 2004; McMurray and Cegielski 2007). A review containing six systematic cohort studies (Lönnroth et al. 2010b) shows a highly consistent linear relationship between the incidence of TB and the level of BMI when BMI is in the normal range (18.5–30 kg/m^2), and that the risk of incidence of TB increased 13.8 % (95 % CI: 13.4–14.2 %) with a one-unit decrease in BMI. However, the study also pointed out that more research is needed to test whether this rule applies when BMI is outside the normal range. A case-control study carried out in Estonia showed that overweight individuals have a lower risk of TB (Tekkel et al. 2002), indicating that high BMI may play a protective role (Hill 1965; McGee and Diverse Populations Collaboration 2005).

The mechanism for the association of malnutrition with an increased risk of TB disease is based on deficiencies of micronutrients and macronutrients having a negative effect on the cell-mediated immune response, thus reducing its ability to eliminate TB (Cegielski and McMurray 2004; McMurray and Cegielski 2007). Two recent studies found that fat tissue can inhibit the replication of *M. tuberculosis*, offering indirect evidence that high BMI may reduce the risk of TB (Neyrolles et al. 2006; Garton et al. 2008).

29.2.4.3 Diabetes

Like TB, diabetes is an important global public health problem. The WHO (2014b) estimated that the global prevalence of diabetes was 9 % among adults aged 18+ years in 2014. The relationship between TB and diabetes is quite clear: the risk of TB in diabetics is three times higher than in nondiabetic patients, and the risk of TB in diabetics follows a dose–response relationship with blood glucose levels. As glycemic control is reduced, the risk of TB increases (Kim et al. 1995). A systematic review of 13 observational studies concluded that diabetes can increase the risk of active TB. Using a random effects model, they found that the combined relative risk of three cohort studies was 3.11 (95 % CI: 2.27–4.26; Jeon and Murray 2008). Another cohort study of 42,116 diabetes patients over the age of 65 supports this conclusion (Leung et al. 2008).

Diabetes can impair the host immune system, leading to damage to the innate and adaptive immune responses that normally restrain the proliferation of the *M. tuberculosis* which leads to TB infection (Jeon and Murray 2008). Because of poor blood glucose control in diabetic patients, protein synthesis is reduced but protein decomposition is accelerated. The result is a reduction in immunoglobulin and complement leading to a reduction in cellular and humoral immune function. In addition, glucose levels in body tissues, blood, and urine all increase. This leads to long-term malnutrition, hypoalbuminemia, and acidosis that can damage the patient's defense mechanisms, induce TB and other bacterial infections, and increase the risk of disease (Wang et al. 2004).

29.2.4.4 Smoking

Large numbers of studies have shown that smoking is an independent TB risk factor (Bates et al. 2007). The risk of TB increases 2.6-fold due to smoking (OR 95 % CI: 2.1–3.4; Slama et al. 2007). Studies have also shown that type and duration of smoking were associated with TB (Ghufron 1994). Compared to non-smokers, passive smokers' OR for TB is 3.4 (95 % CI: 2.0–5.5; Slama et al. 2007), however, the relationship between passive smoking and TB needs to be confirmed (Lin et al. 2007).

Some researchers believe that when nicotine and other harmful substances from tobacco are introduced into the lungs, a complex reaction results to increase the risk of TB. Nicotine can cause the macrophages in a smoker's lungs to turn off production of TNF-α, making it easier for latent TB to progress to active infection (Davies et al. 2006). Some scholars believe that it is biologically reasonable that smoking can increase the risk of TB infection and disease. The possible mechanisms include a weakened immune response, CD4+ lymphopenia, defects in the macrophage immune response, and the reduced airway ciliary clearance of particles (Arcavi and Benowitz 2004).

29.2.4.5 Alcoholism

Alcoholism is, without a doubt, a risk factor for TB and its re-infection (Rehm et al. 2009). Early in the 1950s, a case-control study showed that there was a dose–response relationship between alcohol use and active TB (Brown and Campbell 1961). Research conducted by experts from the WHO Stop TB Partnership, covering three cohort studies and 18 case-control studies, showed that individuals with alcoholism (alcohol intake >40 g/day) or clinically diagnosed with alcohol addiction increased their risk of contracting active TB by two-fold (Lönnroth et al. 2008). Approximately 10 % of active TB cases can be attributed to alcohol (Rehm et al. 2009).

Alcoholism may lead to a high risk of TB incidence because alcohol weakens the immune system, thus increasing the risk of infection. Animal studies suggest that long-term or acute alcohol consumption directly damages the cell-mediated immune response and macrophage function (Mellencamp and Jerrells 1996; Szabo 1997); probably acting indirectly by limiting micronutrients and constant nutrients, or through other alcohol-related disorders such as cancer and depression (Rieder 1999; Prince et al. 2007).

29.2.4.6 Indoor Air Pollution

Currently, there is no certain conclusive evidence that indoor air pollution is related to the incidence of TB. Some studies suggest that exposure to an environment with coal combustion could increase the additional risk of TB (Gupta et al. 1997; Mishra et al. 1999; Pérez-Padilla et al. 2001). However, two review reports do not support this conclusion. Lin et al. (2007) did a systematic review of the impact of smoking and indoor air pollution on the incidence of TB. They found that indoor air pollution caused by biofuel combustion can increase the risk of TB, but in the subgroup analysis, the relationship between these two was not statistically significant after adjusting for confounding factors. A systematic review by Slama et al. (2010) of the relationship between indoor air pollution caused by solid fuel combustion and TB suggested that there is not sufficient evidence to support this claim because sample sizes were too small, and that more research is needed to obtain more convincing evidence.

Although evidence of the relationship between the incidence of TB and indoor air pollution is limited, there is reason to believe that the same mechanism is involved as with smoking-induced TB (Lin et al. 2007). Like tobacco smoke, smoke from solid fuels contains many carcinogens and toxic substances (Slama et al. 2010). Breathing air pollutants (including smoke and dust) damages the normal mucosal surface important in clearance of the trachea and bronchial secretions (Houtmeyers et al. 1999), and the disruption of alveolar macrophage phagocytosis (Sopori 2002) results in the decline of self-purification capacity, thereby increasing the chance of TB infection.

29.2.4.7 Silicosis

Early in the twentieth century, studies discussed the relationship between silicosis and TB (Hnizdo and Murray 1998). Workers exposed to silica dust, whether or not they suffered from silicosis, had an increased risk of TB. In addition, the risk of silicosis patients developing TB was 2.8–39 times higher than in healthy controls, and the relative risk of TB was dependent on the severity of silicosis (Barboza et al. 2008). In China, about 10–30 % of patients with the first stage silicosis have TB. The rates for the second stage and third stage silicosis are 22–30 % and 50–90 %, respectively (Chen et al. 2005).

Patients with silicosis have reduced immunity and lower cellular immune function, increasing susceptibility to TB infection. There is experimental evidence that silicosis can increase the risk of TB disease by damaging the lungs' immune response. Repeated exposure to silica can cause macrophage apoptosis, thus weakening the immune system's ability to phagocytize and kill *M. tuberculosis* (Hong Kong Chest Service/Tuberculosis Research Centre, and Madras/British Medical Research Council 1992; Hnizdo and Murray 1998). Patients with silicosis have high levels of surfactant protein A in bronchial-alveolar lavage fluid, which allows mycobacteria to enter alveolar macrophages without activating the cells' toxicity response, which normally plays an important role in the process of elimination of mycobacteria (Pasula et al. 1999; Gold et al. 2004). It is believed that the retention of silicosis nodules can provide a place for *M. tuberculosis* to adhere, which would increase the risk of infection (Hnizdo and Murray 1998). Conditions associated with silicosis, such as chronic cough, bronchial cilia damage, accumulation of secretions, and/or respiratory defense function decline all create favorable conditions for *M. tuberculosis* invasion. Extensive pulmonary interstitial fibrosis due to silicosis can block blood lymph circulation, and thereby reduce the ability to defend the lung from TB (Xue et al. 2007; Mao 2008).

29.2.5 Contact History

Close contact with active TB cases is necessary for the transmission of *M. tuberculosis* infection. A person's history of contact with active TB cases is a clear risk factor (Lee et al. 2008). A number of studies support this conclusion. A systematic review by Morrison et al. (2008) of 41 studies showed that 4.5 % of TB patient's household contacts were diagnosed with active TB, and 51.4 % were diagnosed with latent TB (LTBI). A hospital based case-control study carried out by Hill et al. (2006) found that 45 % of TB patients had a household contact history of TB, while the proportion in the control group was only 11 %. Lee et al. (2008) conducted a 5-year follow-up study of the close contacts of 4661 TB cases in Hong Kong. In the first 3 months, 31 cases of TB broke out, with another 58 cases appearing later, accounting for 0.67 and 1.24 % of the total number of close contacts, respectively.

M. tuberculosis is airborne and is spread from person to person almost entirely through inhalation of the bacterium (Riley et al. 1962). Whether via a TB patient's

cough or normal breathing process, droplets with bacteria will spread to the surrounding air. Generally speaking, *M. tuberculosis* is not highly contagious. Transmission depends on the combined effects of the pathogen, the environment, and the exposed individual (Styblo 1984), with the distance from the contact and exposure time playing key roles (Morrison et al. 2008). Studies have shown that a classification of contacts can be made, according to the distance and time with the source, which differentiates between active and latent TB. Household contacts are a high-risk group for both latent and active TB (Etkind 2000).

29.2.6 Environmental Factors

The relationship between environment and the incidence is not entirely clear. In the last century, Stein (1954) found that there was a significant relationship between crowded living conditions and the incidence of TB. Recent studies also found that the incidence of TB was higher in communities with a higher density of residents (Clark et al. 2002). Studies in New York, Russia, and Gambia showed similar results (Drucker et al. 1994; Coker et al. 2006; Hill et al. 2006). After adjusting for family income, local TB burden, and the presence of immigrants from high-burden TB nations, the incidence of TB was still significantly associated with crowded living conditions (Baker et al. 2008). However, there are conflicting data. In California, an ecological study on the spread of TB found that after adjusting for confounding factors, overcrowding and TB were not statistically related (Myers et al. 2006). Two studies conducted in South Africa support this conclusion (Coetzee et al. 1988; Schoeman et al. 1991). Although there have been many studies on the relationship between living environment and the incidence of TB, the data does not clearly show the relevance.

It is biologically and environmentally reasonable to theorize that overcrowding can increase the risk of TB. *M. tuberculosis* spreads through nuclear droplets in the living environment (Musher 2003). Living in close contact with others increases the opportunities for susceptible populations to be exposed to TB with an increase in the likelihood of infection (Tornee et al. 2004). Ventilation, humidity, and sanitation of the living environment may also affect the overall health status of the occupants. The living environment also indirectly reflects the family or individual's socioeconomic status, nutritional status, and educational level, which are all associated with the incidence of TB.

29.2.7 Socioeconomic Factors

Many countries have carried out studies on the effects of socioeconomic factors on the incidence of TB, but the conclusions vary because of the different factor definitions, time periods, and populations in different countries (Colditz et al. 1994) Socioeconomic factors are often linked with other risk factors. For example, poverty

is often accompanied by malnutrition, overcrowding, poor medical services, and low levels of education. The following section will focus on the relationship between the incidence of TB and poverty, migration, and social change. All of these factors have an impact an individual's exposure and immune system.

29.2.7.1 Poverty

Poverty is defined as material, social, and emotional deprivation. This includes lack of economic resources, education, and basic living guarantee. There are two kinds of poverty: absolute poverty and relative poverty. Absolute poverty is associated with malnutrition, disease, illiteracy, unsanitary environments, high infant mortality, and low life expectancy. Relative poverty is related to the overall development of a particular society (Benatar and Upshur 2010).

Although defined differently and evaluated based on a variety of poverty indicators, it is clear that poverty is an important risk factor in the incidence of TB (Yang et al. 2009). Research on the relationship between poverty and TB is mainly conducted at the population level, most of which supports the idea economic status is an important risk factor for TB (Hawker et al. 1999; Barr et al. 2001; Clark et al. 2002; Russell 2004; Myers et al. 2006). In fact, some scholars believe that poverty is the main driving force for the existence and spread of TB (Benatar and Upshur 2010). One of the most representative studies was conducted in New York on changes in the incidence of TB at the city level. Results showed that poverty in neighboring areas was an important factor in the rise of the epidemic in New York City between 1984 and 1992 (Barr et al. 2001). Studies based on a macro-level showed that in Europe, the more equal the distribution of wealth in an area, the lower the incidence of TB (Suk et al. 2009). Studies by Arinaminpathy and Dye (2010) found that during the recession in the 1990s, 15 Eastern European countries were found to have a strong correlation between widespread recession and TB incidence. A study in Estonia found that compared to average income levels, adjusted OR for the lowest monthly income level was 9.86 (95 % CI: 2.21–43.89) and for non-fixed-income was 12.30 (95 % CI: 3.19–47.35) (Tekkel et al. 2002). Though these studies confirmed that poverty is related to TB, studies in other populations found no significance in the relationship between the two (Grange et al. 2001; Nishiura 2003).

29.2.7.2 Immigration

Since the 1980s, human migration has reached an unprecedented scale (Menzies 2000). Mass migration has occurred from high TB incidence countries to low TB incidence countries (Dasgupta and Menzies 2005). There is no conclusive evidence showing that immigration from high incidence TB countries affects incidence in the lower TB incidence countries (Arshad et al. 2009). However, some studies suggest that immigrants had the highest risk of TB within the first few years of emigration (MacIntyre et al. 1993; MacIntyre and Plant 1999). The incidence of TB in a migrant

population will decline significantly as time goes by, but generally is still higher than that of local residents (Cain et al. 2008). Today, in Western Europe and North America, more than half of new active TB cases are from foreign-born immigrants (Dasgupta and Menzies 2005). An ecological study conducted by Myers et al. (2006) in California showed that the risk of TB in foreign-born immigrant children (0–14 years) is 1.26 times that of the US born children (95 % CI: 1.14–1.40). However, studies in some European countries did not confirm this result. For example, a study in Estonia found that the TB disease risk of immigrants and native populations was similar or even lower, adjusted OR was 0.51 (95 % CI: 0.27–0.99; Tekkel et al. 2002). Researchers believe that immigration is not a major risk factor for the occurrence of TB (Raitio and Tala 2000).

29.2.7.3 Social Changes

Large changes in human society have great impact on the incidence and spread of TB. During war and post-war periods, the morbidity and mortality of TB increases significantly (Barr and Menzies 1994). Global travel for international exchange projects, vacation, study, work, and residence has become a universal phenomenon. As the economies of developing countries promote rapid social and economic growth, more and more migrant workers move into cities for job opportunities. Populations are maintaining a growth trend, and at the same time society is gradually aging. It is estimated that by 2025 the number of people aged 60 and over will reach 1.2 billion, and by 2050 that number will be two billion, 80 % of which will be from developing countries (WHO 2002).

These great social changes create both challenges and opportunities in the fight to prevent and control TB. TB is a poverty disease. As economic development continues, people's living condition should improve along with improvement in health services and their distribution. However, large-scale population movement and aging populations are challenges to TB prevention and control. Because effective evaluation and quantification of these factors would require enormous manpower and large financial expenditures, quantitative research in this area has not been published. However, changes in global social structure should be brought to the forefront for policy-makers and TB prevention and control personnel so that the promise of "a world without TB" can come true.

29.2.8 Contributing Factors for the Incidence of TB in High-Burden TB Countries

Although many factors can increase the risk of TB, their contributions to the incidence of TB are not equal. Population attributable fraction (PAF) is a statistic used to evaluate the contribution of exposure factors to diseases. It represents the

Table 29.1 Population attributable risk factors (PAF) in 22 high-burden TB countries (Lönnroth et al. 2010b)

	Relative risk of active TB (RR)	Weighted prevalence (%)	PAF (%)
HIV infection	20.6/26.7	0.8	16
Malnutrition	3.2	16.7	27
Diabetes	3.1	5.4	10
Alcohol abuse (>40 g/day)	2.9	8.1	13
Smoking	2.0	26.0	21
Indoor air pollution	1.4	71.2	22

contribution of a risk factor to the cause of a disease, or the extent that the incidence will be reduced if you eliminate the factor. When the exposure rate rises, PAF will increase as well. PAF has a great significance in public health and disease prevention as a guide to optimize the allocation of limited health resources (Li 2004).

Lönnroth et al. (2010b) calculated the PAF of risk factors for the incidence of TB in adult populations in 22 high-burden countries (Table 29.1).

Note that silicosis is not listed though the relationship between silicosis and TB is clear. The incidence of silicosis in the whole population is very low, as it only occurs in specific groups of people exposed to dust. So its contribution to the incidence of TB in large populations is small.

29.3 Intervention Strategies and Implementation of Factors for TB

Currently, the WHO International Union Against Tuberculosis and Lung Disease (The Union) and other relevant organizations have proposed recommendations regarding the factors affecting TB incidence as well as prevention and control strategies. Strategies have been formulated for TB/HIV co-infection, TB and diabetes control, tobacco control, prevention and control of TB and close contact with TB patients, or from recommendations for implementation of other aspects of TB prevention and control strategies.

29.3.1 TB/HIV Co-infection

In 2013, the WHO estimated there were 1.1 million HIV-positive patients among the nine million emerging TB patients. This accounted for 12 % of the total number of new TB patients, and 78 % of these co-infected patients live in sub-Saharan Africa (WHO 2014c). Since 2006, the number of HIV-positive TB patients, the proportion of new TB patients, and the number of HIV-positive TB patient deaths

have all significantly increased. Only the proportion of HIV-positive TB patients in sub-Saharan Africa has decreased (by 5 %; WHO 2008a).

The United Nations Millennium Summit set the Millennium Development Goals in 2000. One of the goals was to halt and reverse the incidence of TB by 2015. On this basis, the Stop TB Partnership proposed that, by 2015, TB prevalence and death rates be decreased by 50 % compared with 1990 averages and the AIDS epidemic and its spread be stopped. Additionally, the Stop TB Partnership aimed to reduce the global incidence of active TB to 1/1,000,000 by 2050 (WHO Regional Office for Africa 2004; Stop TB Partnership 2010).

The WHO established the global TB/HIV Working Group in 2001, which issued a Reduce TB/HIV burden Strategy Framework in 2002. After several international meetings and discussions, the WHO released Interim policy on TB/HIV collaborative activities (WHO 2004) to promote TB/HIV co-operative activities. The goal was to reduce TB/HIV dual infection and the burden of TB and HIV.

The following are three specific aims of the WHO's TB/HIV co-infection prevention and control strategies (WHO 2012):

Establish a mechanism to control HIV and TB co-infection by establishing an organization to effectuate cooperation between countries and between non-governmental organizations (NGO), implementing HIV virus monitoring in TB patients, developing a TB/HIV joint plan, and implementing epidemiological surveillance and evaluation.

Reduce the burden of TB in AIDS patients by implementing the 3I strategy, which includes *I*ntensified TB case finding, *I*soniazid preventive therapy (IPT), and ensuring *I*nfection control in health facilities.

Reduce the burden of HIV in TB patients by offering counseling and testing, carrying out HIV preventive activities and co-trimoxazole preventive treatment, ensuring HIV care and support, and promoting antiretroviral treatment.

29.3.1.1 HIV Prevention and Control Strategies in Highly Endemic Areas

AIDS is highly prevalent in Africa, and although modern TB control strategies have been adopted, TB incidence in the sub-Saharan region presents an unprecedented rate of increase, especially in high HIV prevalence areas. There is evidence that attributes this to the HIV epidemic. For this reason, the WHO Africa Regional Office issued the *African TB/HIV Control Strategy* (2004) to further strengthen the goals, objectives, and measures of developing TB/HIV collaborative activities in Africa. The TB/HIV prevention and control strategies developed and implemented in Africa include:

- Enhancement of health system capacity and creation of a favorable environment
- Prevention of TB, HIV, and sexually transmitted diseases
- Delivery of care and support activities for HIV-positive patients and TB patients
- Carrying out community mobilization and ensuring continuation of activities

29.3.1.2 HIV Prevention and Control Strategies in Low and Average Endemic Areas

In the Western Pacific, where the prevalence of HIV is relatively low, implementation of TB/HIV collaborative activities is relatively limited. In order to expand response measures, the WHO Western Pacific Regional Office (2011) issued a *Western Pacific Regional Strategy to Stop TB (2011–2015)*. The report made it clear that all countries in the Western Pacific region have to develop and strengthen TB/HIV collaborative activities. In it, they established three core goals for stopping TB, as follows:

- TB programs should offer HIV testing for all TB patients and provide CPT and ART treatment for all TB/HIV co-infected patients in accordance with recognized standards of care
- AIDS programs should use the 3I strategy. TB programs should collaborate with HIV programs and implement TB screening for people with HIV as standard care. After elimination of active TB, TB/HIV dual infection patients should be treated with isoniazid preventive therapy (global target rate: 50 %).
- TB and HIV programs should develop a jointly implemented and monitored plan on TB and HIV control activities.

29.3.1.3 Implementation of TB/HIV Prevention and Control Strategies

From 2005 to 2009, the proportion of TB screening in the global HIV-positive population increased from 0.6 to 5.2 % and reached 18.9 % in 2014 (WHO 2015). Among the 49 countries that reported data for 2014, IPT was provided to more than 930,000 people living with HIV, up from around 600,000 receiving it in 2013 (WHO 2015).

29.3.2 Diabetes

Although the relationship between diabetes and TB has been well documented, prevention and control strategies are still in the research and discussion stages and clearly established measures for prevention and control for dual diagnosed patients have not been developed. Emerging trends in TB/diabetes dual diagnosis have convinced countries with a high burden of TB and of diabetes to consider integrating the management of both diseases. The Harvard School of Public Health completed a bidirectional systematic review of TB and diabetes screening (Jeon et al. 2010). Using meta-analysis of 30 relevant studies, they reported that screening TB patients for diabetes and diabetes patients for TB leads to the detection of more cases of dual diagnosis.

29.3.2.1 TB/DM Framework

The World Diabetes Foundation (WDF) and The Union, through the WHO's Stop TB Partnership, discussed prevention and control strategies for TB and issued the provisional *Collaborative Framework for Care and Control of TB and Diabetes* (WHO and The Union 2011). However, the policies and measures of the framework still need to be verified through on-site implementation. The provisional TB/DM framework is similar to the TB/HIV strategy, in that it is based on the needs of TB prevention and control (WHO and The Union 2011). The following are included:

- Screening for TB in diabetes patients; screening should be conducted at least in high TB epidemic areas.
- Screening for diabetes in TB patients and providing diabetic patients with high-quality services following the DOTS model for treatment.
- Extending diabetes prevention and care through the TB programs advocacy mode.
- Enhancing health system capacity through cooperative activities.

29.3.2.2 Expected Result of TB/DM Prevention and Control Strategies

In TB/DM framework of two-way screening for TB and diabetes, about 1.7–36 % of diabetic patients are expected to be suffering from TB. This ratio increases as the local severity of TB and diabetes increases. About 1.9–35 % of TB patients are expected to be diagnosed with diabetes (Jeon et al. 2010).

29.3.3 Tobacco

While tobacco consumption in high-income and middle-income countries is declining, global tobacco consumption has increased (WHO 2011a). Between 2005 and 2006, worldwide smoking rates increased in males over the age of 15 from 38.7 to 41.1 % and in females from 7.4 to 8.1 % (WHO 2008b, 2011b). The number of passive smokers increased from 208 million in 2007 to 362 million in 2008, an increase of 74 % (WHO 2011a).

The relationship between tobacco and TB has been clearly established. Tobacco control strategies developed by the WHO not only include a global tobacco control treaty, but also recommend prevention and control strategies for TB and tobacco.

In 1995, the WHO proposed the idea for an international instrument for tobacco control, which became the prototype for the International Convention on Tobacco Control. At the 56th World Health Assembly in 2003, 192 WHO member states unanimously adopted the first global convention on tobacco. The *Framework Convention on Tobacco Control* (WHO 2005b), which outlined clear measures for reducing demand for tobacco and the tobacco supply, went into effect on February

27th, 2005. This Framework Convention is the first United Nations legally binding multilateral public health treaty, which provides legal protection of human health from tobacco hazards through jointly implemented global safeguards.

29.3.3.1 WHO Recommended Tobacco-Related TB Prevention and Control Strategies

The WHO, through its Tobacco Free Initiative, cooperated with the Stop TB Partnership and The Union in 2004 to integrate tobacco control and respiratory disease health services in primary health organizations. The goal was to evaluate whether these measures would enable patients with respiratory disease to reduce smoking and thereby reduce their risk of TB (WHO and The Union 2007).

The first stage adopted systematic review methods to determine whether there was a causal association between the incidence of TB and smoking. In 2005, through analysis of 50 eligible studies, it was confirmed that the incidence of TB and smoking were related.

The second stage was to develop strategies for providing guidance to program managers for both national tobacco and TB control programs for carrying out joint activities in tobacco control in the framework of existing TB strategies in the health service systems. The strategy was to determine the smoking status of suspected TB patients (or patients with other respiratory diseases) being treated in primary healthcare services and provide counseling and smoking cessation treatment.

The WHO recommended strategies for tobacco and TB prevention and control includes the following seven recommendations (WHO and The Union 2007):

- Control tobacco, especially in areas with high incidence of TB.
- Coordinate national TB and tobacco control programs.
- Provide cross-training for TB and tobacco control healthcare workers.
- Identify TB patients that smoke and provide counseling and treatment.
- Promote and implement smoke-free policies, especially in locations that provide TB services.
- Incorporate the tobacco intervention programs The 5 A's and The 5 R's into TB control program operations. The 5 A's are: *A*sk TB patients if they smoke, *A*dvise patients to quit, *A*ssess the willingness of patients to quit, *A*ssist the patient in their attempt to quit, and *A*rrange follow-up. The 5 R's are: *R*elevance: let patients know that quitting smoking will make TB treatment more effective; *R*isks: point out the hazards of continued smoking, including the risk of recurrence of TB; *R*ewards: inform patients of the benefits to quitting smoking; *R*oadblocks: identify the barriers to smoking cessation to patients; *R*epetition: repeatedly encourage TB patients to stop smoking.
- Carry out smoking cessation activities through the implementation of the Practical Approach to Lung Health: performing patient-centered diagnosis and treatment of common respiratory diseases in primary care, promoting integrated care management based on symptoms, and striving for a high level of service through the development and implementation of clinical guidelines.

29.3.4 Close Contacts

In 1962, it was proven that isoniazid prevented TB infections in household contacts of TB patients (Ferebee and Mount 1962). Investigation and treatment of latent TB infections in contacts became an important strategy for controlling and eliminating TB (Hsu 1963; Simone 1995). The American Thoracic Society (ATS) released brief guidelines on the investigation, diagnostic evaluation, and treatment of TB contacts in 1976 (Iseman et al. 1976). The guideline was updated in 2003 (American Thoracic Society et al. 2003).

The National Tuberculosis Controllers Association (NTCA) and CDC jointly released the updated *Infectious Tuberculosis Patient Contact Investigations Guide* (2005). It was based on a review of epidemiological and other related research and on normal contact investigation practices. Guidelines offer recommendations for the investigation of TB contacts and for the treatment of infections, including:

Investigation of TB contacts. Investigation of the contacts of sputum smear- or culture-positive TB patients is considered the highest priority. Investigation of contacts should also be considered if the patient does not fit the previous criteria but chest X-ray features are consistent with TB.

Collection of index patient and transmission site information. The patient's full information is the basis of the contact investigation. This information includes TB disease characteristics, onset time, contact names, exposure location, and current medical factors (such as start-up of effective treatment and sensitivity test results).

Determination of the priority of contacts. According to the characteristics of the TB patient, susceptibility and vulnerability of the contacts, and exposure circumstances, contacts will be classified as high-priority and medium-priority contacts.

Diagnostic and public health assessment of contacts. Within 3 working days of the contact being included in the survey, the investigators collect basic health information and conduct a face-to-face assessment of the contact's health status. A skin test should be done on contacts who are classified as medium or high priority in the initial meeting. If medical documents show that the contact had a positive tuberculin skin test in the past or had a previous history of TB, a track test should be given at the end of the window period (8–10 weeks after exposure). All individuals with skin test reaction indurations with a diameter of 5 mm or more, or individuals who have suspicious symptoms of exposure to TB, should receive further examination and diagnostic tests for TB, such as a chest X-ray. All high-priority contacts, regardless of skin test results or symptom presentation, should be given further examination and diagnostic tests.

Treatment of contacts with Latent TB Infection. It is recommended that susceptible and vulnerable contacts are treated to prevent the rapid onset of TB during the window period. After the exclusion of TB, those with latent infections based on a positive skin test and those with a history of TB and HIV-positive contacts should receive treatment.

29.3.4.1 Effect of Prevention and Control

Studies have shown that investigations of contacts of pulmonary TB patients are useful in identifying additional TB patients. Four percent of TB patients are identified through contact investigation (He et al. 2007).

29.4 Conclusion

In-depth research has been conducted on the factors affecting the incidence of TB. Although some factors have been clearly identified, the relationship between other factors and TB needs further investigation. The WHO, The Union, and other relevant international organizations have developed recommendations for prevention and control strategies dealing with known and suspected risk factors. However, countries and regions should adapt or revise these strategies in accordance with their national and regional needs, local realities, and in consideration of existing available resources.

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Chapter 30
DNA Fingerprinting of *Mycobacterium TB*: A Rich Source of Fundamental and Daily Applicable Knowledge

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30.1 Introduction

It is estimated that one-third of the world's population is latently infected by *Mycobacterium tuberculosis (M. TB)*. According to WHO surveillance, though the incidence of tuberculosis (TB) has been in decline since 2004, the absolute number of cases is still increasing owing to the steadily expanding human population. Strongly contributing to the increase of the TB problem are co-infections with HIV and the emergence of *M. TB* strains resistant to the currently used anti-TB drugs. In order to control TB, it is highly important to understand the natural history of TB infections in different settings. Moreover, it is relevant to investigate transmission of TB at national and international levels and to associate this to risk factors. Last but not least, phylogenetic studies highlight the population structure of *M. TB* and its ongoing evolutionary changes that influence the TB epidemic by the emergence of resistance and presumably higher ability to circumvent vaccine-induced immunity.

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30.2 Molecular Typing Techniques for the *M. TB* Complex

In the 1980s, pioneers like Collins and De Lisle explored the use of restriction fragment patterns to compare *M. TB* in epidemiological studies (Collins and De Lisle 1985). In this period, phage typing was the only meaningful but restricted epidemiological typing available although some researchers also utilized resistance profiles as markers in the epidemiology of TB (Gruft et al. 1984). In the early 1990s, molecular typing of *M. TB* was developed based on the detection of DNA polymorphism associated with repetitive sequences. Since then, several DNA fingerprinting methods have been developed with different levels of reproducibility, stability, discriminative power, and demands on technical expertise (Kremer et al. 2005). Initially, IS*6110* restriction fragment length polymorphism (RFLP) and spoligotyping were the most widely applied and internationally standardized techniques. In recent years, the 24-locus Variable Number of Tandem Repeat (VNTR) typing has gained recognition as the new international standard method in the molecular epidemiology of TB. All DNA fingerprinting markers have different molecular clocks, that is, they change at different rates. The stability of DNA profiles has been studied extensively and acts in a stochastic manner, but it is not fully understood (de Boer et al. 1999). It is clear, however, that the pace of molecular change is not in range with the transmission cycle of TB. Ideally, at each transmission, a slight change should occur in a DNA fingerprint, while the characteristic footprint of the strains can still be recognized. In that way, primary sources in a chain of transmission could be distinguished from the subsequent sources, making a much more detailed analysis of transmission in a given area possible. Recent application of whole genome sequencing of *M. TB* isolates for the visualization of transmission chains among isolates in DNA fingerprint clusters has shown that this approach may add significantly to our currently used fingerprinting methods (Schurch et al. 2010).

Spacer oligotyping or spoligotyping (Kamerbeek et al. 1997) is a simple tool to study the phylogeny of *M. TB* and the worldwide spread of genotype families. The level of discrimination of spoligotyping is, unfortunately, generally low and one has to be cautious using this method to examine transmission of TB on strain level (Kremer et al. 2005; van der Zanden et al. 2002).

From the early 1990s until recently, IS*6110* (RFLP) typing (van Embden et al. 1993) served as the gold standard in typing of individual *M. TB* isolates. It has been used extensively since 1993 because of its high level of discrimination (Kremer et al. 2005), reproducibility, and the fact that this was the first DNA strain typing method suitable for studying transmission at various levels (van Soolingen 2001).

The half-life of IS*6110* RFLP was estimated to be 3–4 years (de Boer et al. 1999). This means that on average, half of the strains exhibit a band shift in their IS*6110* RFLPs in a 3–4-year period. This interval seems useful for distinguishing epidemiologically related and unrelated isolates and therefore supports the use of IS*6110* typing in epidemiological studies of recent transmission of TB (van Soolingen 2001).

Since the introduction of variable numbers of tandem repeats (VNTR) typing for *M. TB* complex isolates in 1997 (Supply et al. 1997), this technique was steadily improved by the incorporation of high performance loci and therefore it gradually replaced IS*6110* RFLP as the gold standard (Prodinger 2007). In 2006, a 24 loci VNTR typing was proposed as the new international typing standard (Supply et al. 2006).

30.3 Use of DNA Fingerprinting to Support Contact Tracing

Different factors contribute to the ongoing transmission of TB. A strong association for the transmission of TB in a low-prevalence setting is observed with male sex, urban settings, and lower age of the source case (Borgdorff et al. 2001). TB cases detected in Europe were predominantly male and the median age was 43 years. Patients with a previous history of TB were more likely to be infected with multidrug-resistant (MDR) strains, which is also a major risk of death (Lefebvre and Falzon 2008).

One of the most important applications of molecular strain typing is the support of DNA fingerprinting information to contact tracing and source case finding. This can only work if three factors for optimal use of genotyping data are available: a proper public health system, reliable genotyping data, and the willingness to integrate both (Prodinger 2007). However, one has to bear in mind that identical DNA fingerprints of isolates indicate a possible transmission between patients, but do not prove such transmission. In any case, the availability of clustering data will increase the detection of epidemiological links and therefore, genotyping has a positive predictive value for the detection of epidemiological links (Lambregts-van Weezenbeek et al. 2003).

Even in settings with a good functioning contact tracing, DNA fingerprinting surveillance is far superior in tracing presumable epidemiological links than tracing of contact by interviews according to the stone in the pond principle (Veen 1992). From data spanning 1993 to 2011 in the Netherlands, only about 50 % of the epidemiological links detected by DNA fingerprinting would have been confirmed or considered likely in contact tracing by interviews alone (unpublished observation). Although unsettling, this is not difficult to understand; many of the transmissions take place outside of regular contacts and through instant and brief contact and will not be remembered by the persons involved. Assuming the sources of infection and secondary cases need to know each other or at least should share known places where they could have met is an underestimation of the mobility and flexibility of human behavior.

Genotyping is therefore a highly important tool to investigate the natural history of the TB infection. In fact, to facilitate an effective TB control program, one should determine for all cases what the source of transmission was. In the study of de Vries et al. (2009) in the harbor city of Rotterdam in the Netherlands, all cases were assigned to different categories regarding the origin of infection. Finding the source

is essential for control. First, a transmission event, suspected from contact tracing results, may become either confirmed (by identical fingerprints) or demonstrate otherwise (by different patterns) even before contact tracing is performed. Second, the addition of DNA fingerprinting to conventional contact tracing may indicate unsuspected transmission of TB at different levels, and in some situations it could be used to reconsider the direction of conventional contact tracing. This is especially important in countries with low prevalence of TB, where the elimination of this disease comes into sight (Crawford 2003; Martin et al. 2009; Prodinger 2007; van Soolingen 2001). If it is not possible to eradicate TB, at least the origin of transmission should be traced by application of routine DNA fingerprinting of *M. TB* isolates.

Over time, a large part of the DNA fingerprint clusters are abortive. However, some grow to considerable sizes of more than 100 cases through the years. It is therefore tempting to investigate whether particular characteristics of clusters can be used to predict which clusters are prone to grow, as they are associated with ongoing transmission. For instance, patient age, nationality, residence, and risk factors like being homeless are variables that are known shortly after the diagnosis of a new TB cluster and some characteristics have been found to be associated with clustering. However, recently, two factors appear to be useful to indicate whether contact tracing should deserve more attention than on average. If there is a short time period of less than 3 months between the first and the second case in a DNA fingerprint cluster, this is a good predictor of cluster growth to at least 5 cases within 2 years (Kik et al. 2008). In a recently published study, a correlation was found between the size of the DNA fingerprint cluster and the average number of positive contacts found around the individual cases in contact tracing (Verhagen et al. 2011). This correlation was independent from the time a case was diagnosed. The cases found early in the establishment of a large cluster showed the same trend as the ones found years later. This implies it is useful to have a look at the size of the cluster a case is added to; if is relatively larger, there is a larger chance more positive contacts around this case will be traced.

In summary, the application of genotyping provides important insight into TB transmission in a given area and is of added value for the performance of conventional epidemiological investigation (Sintchenko and Gilbert 2007; de Vries et al. 2009).

30.4 Recent Transmission Versus Endogenous Reactivation

In the early 1990s, with the increase in the incidence of TB in several cities in the USA like San Francisco and New York, it was not well known what caused this unexpected rise in the rates. On the basis of DNA fingerprinting, however, it became clear that active transmission was a major factor (Small et al. 1994).

After some years of routine application of DNA fingerprinting in these low prevalence settings, it became clear that clustering of cases is strongly age dependent

(Yang et al. 1995). Low aged cases are almost invariably in clusters and this is logical, as they contracted their infection recently and the fingerprint of the isolate of the source of infection is also present in the database. With the increase in age, the chance increases that the disease is due to an endogenous reactivation of a remote infection, and this is reflected in the almost linear inverse correlation between the percentage of clustering cases and age (van Soolingen et al. 1999; Vynnycky and Fine 1997). Moreover, several studies have shown that clustered cases are more frequently of the same age category (ten Asbroek et al. 1999; Borgdorff et al. 2010) and this implies that TB transmission in, for instance, the Netherlands is mainly from young to young individuals (Borgdorff et al. 2001). This may have important implication for studies on the population structure of *M. TB*. Cases in the higher aged category reflect the population of bacteria circulation in the past although a subset of *M. TB* genotypes may be prone to go into a dormant state, and this may obscure this observation. Strains isolated from young people reflect the ongoing transmission and detail the real-life situation regarding the population structure of *M. TB*. If this assumption can be extrapolated to high prevalence settings, this facilitates studies on the dynamics in the population structure of *M. TB* in a given area. Most pronounced in this respect are the studies on the occurrence of the Beijing genotype. In Vietnam, but also worldwide, significant correlations between the Beijing genotype and low age of being observed suggests this genotype is emerging (Anh et al. 2000; Buu et al. 2009; Glynn et al. 2002). This is especially alarming since multiple publications suggest the Beijing genotype is also correlated with multidrug resistance (Devaux et al. 2009, 2010; Glynn et al. 2002).

30.4.1 The Role of Exogenous Reinfection

Especially in high prevalence areas, relapses after curative treatment play an important role. In such cases, it was previously unclear whether the relapses were caused by treatment failures and hence by the same bacteria, or whether they were caused by exogenous reinfections by new strains. This distinction is highly important, since treatment failures demand different measures than reinfections. If the *M. TB* isolates from both episodes are available, DNA fingerprinting can make the distinction between the two possible causes of relapses. On the basis of DNA fingerprinting, in South Africa, not less than 77 % of the relapses after curative treatment appeared to be caused by reinfections (Verver et al. 2005). Most likely, the percentage of reinfections is related to the general risk of TB infection in a given area. The observed level of reinfection challenges the possibility of developing a new, more effective vaccine. If a natural infection does not protect against a subsequent infection, a non-natural and stronger immunological response should be induced in comparison to the natural situation.

30.4.2 Cross-Contaminations and Other Diagnostic Mishaps

During the process of sampling of clinical specimens and processing in the laboratory, many mistakes can occur although an adequate quality assurance program will limit this significantly. For instance, contaminated bronchoscopes and incorrectly labeled specimen containers are the first suspects for the occurrence of errors. At the laboratory site, incorrect labeling, sample exchange, cross-contamination, and administrative mistakes can be the cause of errors. In some of the cases, DNA fingerprinting can be an important aid to visualize these diagnostic failures. For instance, if in one laboratory within a sampling period of 1 week, two isolates are identified with the same DNA profile, this may be an indication of a sampling or laboratory error. In such instances, the involved laboratory should be asked to check the series of samples handled, the bacterial load of the original specimen in comparison to the positivity of the culture and the procedure of transport preparation, in order to confirm or reject the possible laboratory cross-contamination. In addition, the clinician can confirm or reject the clinical TB suspicion of the patients involved in the possible contamination episode.

Regular comparisons of the DNA fingerprints of *M. TB* strains isolated in a given laboratory is helpful in this respect, and improving the quality assurance regarding diagnostic procedures (Martinez et al. 2006) is recommended to decrease the number of false-positive diagnoses of TB. In the Netherlands, with a very low prevalence of TB (7/100,000), about 3 % of the positive cultures are derived from subsequently confirmed cross-contaminations (van Soolingen 2001), which correspond with the range of 0.9–3.5 % reported earlier by McNabb et al. (2002).

The consequences of false-positive TB detection should not be underestimated. Patients that are falsely assumed to be positive for TB incur unnecessary treatment and raise their risks of exposure to TB from public health workers.

The implementation of VNTR typing may contribute to a faster detection of possible laboratory cross-contamination compared to the previously used RFLP typing method, and this may reduce the impact of a false-positive diagnosis of TB (Martin et al. 2008).

Because routine application of DNA fingerprinting is almost invariably restricted to low prevalence settings, the rate of cross-contamination in high prevalence settings should be investigated. This can be easily observed by comparing the typing of all successive isolates on consecutive days. If a series of isolates with identical fingerprints are traced, this warrants further investigation.

30.4.3 Transmission of Resistant TB

There is a long lasting debate on the fitness of resistant *M. TB*. In the 1960s, it was known that isoniazid (INH)-resistant bacteria in general were less virulent in a guinea pig model. Routine application of DNA fingerprinting made it possible for

the first time to study the transmissibility and breakdown of disease in relation to resistant phenotypes and mutations underlying the resistance. In the Netherlands, it was observed that INH resistance is in general a negative risk factor for transmission followed by breakdown to disease, while strains with a mutation at amino acid 315 of the *katG* gene are just as transmissible as susceptible strains (van Doorn et al. 2006; Hu et al. 2010; van Soolingen et al. 2000). This *katG* 315 mutation was also associated with poly resistance and a higher level of INH resistance compared to other mutations underlying INH resistance. This seems to indicate the reduction in fitness due to INH resistance is dependent on the type of resistance conferring the resistance. This is conceivable, as the expression of *katG* is both involved in the intracellular activation of INH and the defense of *M. TB* against exposure to intracellular oxygen radicals released by immune cells like macrophages. Also, the fitness of *M. TB* with mutations in the *rpoB* gene has been studied and this also varies by mutation. Rifampicin-resistant *M. TB* with the mutation S531L in the *rpoB* gene appeared to have restored the highest level of fitness in comparison to mutants with other mutations (Gagneux et al. 2006). Consequently, MDR-TB isolates with the amino-acid change S315T of the *katG* gene and S531L of the *rpoB* gene (Borrell and Gagneux 2009; Gagneux et al. 2006) most likely have the highest fitness and, hence the highest transmissibility and breakdown to disease and that is what we indeed observe in the daily practice. In Europe, there is an ongoing study on international transmission of MDR strains. Of the 1356 VNTR patterns analyzed from the period of 2003 to 2009, almost half were in DNA fingerprint clusters. In total, 67 % of the clustered cases were due to transmission for one MDR-TB strain characterized by identical VNTR profiles: the S315T mutation in the *katG* gene and the S531L mutation in the *rpoB* gene (unpublished observation).

30.5 Studies on the Phylogeny of *M. TB*

From the extensive use of several DNA fingerprinting methods, genotype families have been described. The first one was the Beijing genotype family, most widespread in South-East Asia, but also prevalent in the former Soviet Union States, South Africa, and particular Northern American cities. Although IS*6110* RFLP can be used to recognize the genotype families to some degree, spoligotyping is more robust to identify different clades in the *M. TB* complex. A better phylogenetic tool is the detection of large genomic deletions and, based on this, a robust phylogenetic tree has been established by R. Brosch et al. (2002). Most reliable, however, is the use of single nucleotide polymorphisms to mark unidirectional points in the evolutionary development of these bacteria (Hershberg et al. 2008). Due to the ease and low cost, spoligotyping has been used most extensively to examine the distribution of genotype families in many geographic areas. At Guadeloupe, a database of spoligo patterns is held already comprising 1939 spoligo patterns representative of circa 40,000 strains (Brudey et al. 2006). The research on the phylogeny of *M. TB* may yield important conclusions regarding the evolutionary development of this

bacterium. *Mycobacterium canetti*, with the lowest number of large genomic deletions and invariably traced back to the Horn of Africa, may resemble the highest degree of similarity with the ancestor of the whole *M. TB* complex (Fabre et al. 2010), and in the long run this may provide theories on how *M. TB* adapted to the human host. The widespread Beijing genotype is emerging in several parts of the world and in multiple areas it is associated with multidrug resistance (Anh et al. 2000; Glynn et al. 2002; Streicher et al. 2004). More studies are needed on the dynamics in the population structure of *M. TB* and the possible correlation between genotypes and other factors like transmissibility and expression of the disease. If there is an evolutionary change in the worldwide population of *M. TB*, this may have serious consequences for the development of the TB epidemic in the coming years.

30.6 Future of the Molecular Typing of *M. TB*

Nowadays, typing techniques based on the IS*6110* element and variable numbers of tandem repeats contribute to a better understanding of many aspects regarding TB. However, these markers have their limitations for the questions of the future. Recent applications of whole genome sequencing of *M. TB* isolates for the visualization of transmission chains among isolates in DNA fingerprint clusters has shown that this approach may add significantly to our currently used fingerprinting methods (Gardy et al. 2011; Schurch et al. 2010). Therefore, genome sequencing may become the new standard for typing *M. TB* in the future. The higher discriminatory power, the additional information including mutation detection in genes associated with drug susceptibility, and genotype identification are all advantages of whole genome sequencing. The price of whole-genome sequencing is decreasing, but for a diagnostic setting, the costs have to be much lower. Data-analysis and data storage are new challenges that have to be met.

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Chapter 31
A Case Study: China—Implementation of Nationwide TB Epidemiology Surveys and Estimation of TB Incidence

Shiming Cheng

31.1 TB Epidemiological Sampling Surveys in China

The Ministry of Health (MoH) of China held a national conference on tuberculosis (TB) prevention and control in Liuzhou City, Guangxi Autonomous Region, in May 1978. At the conference, a MoH official gave a keynote speech on "Focusing on the prevention and elimination of TB to contribute to the modern development of China." In addition, the participants discussed and reached consensus on the 1978–1985 *National TB Control Program* (NTP) which aimed to reduce the TB prevalence in all provinces, autonomous regions, and municipalities by 1985 compared to the 1978 levels. Due to the absence of nationally standardized survey methods and protocols, or a standardized morbidity survey, nationwide TB epidemiological data were not available at that time. Therefore, the conference proposed a nationwide TB epidemiological sampling survey. As a result, the first nationwide TB epidemiological sampling survey was launched in 1979.

31.1.1 First National TB Epidemiological Sampling Survey (1979)

The first nationwide TB epidemiological sampling survey made use of stratified, disproportionate cluster random sampling. This involves dividing the population into homogeneous subgroups and then taking a simple random sample in each subgroup using different sampling fractions in the strata. The survey sites were divided between the provinces and autonomous regions and the municipalities and prefectures. A

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"cluster" means that all survey subjects at the survey sites were covered by the survey. Approximately 1500 persons were included at each survey site. In most provinces, there were approximately 32 survey sites, averaging about 50,000 people surveyed per province. For provinces with a population larger than 50 million, the number of survey sites would be increased as appropriate; for provinces with a population smaller than ten million, the number of survey sites would be decreased as appropriate, but not less than 20. The total number of survey sites sampled reached 888.

Survey methods included the collection of general information on the sex, age, TB contact history, and TB history of the survey subjects. Children under the age of 15 years at the survey sites and all people at some survey sites where bacille Calmette-Guérin (BCG) inoculation was not carried out received PPD skin tests. People over the age of 15 years and children with positive PPD skin test results received chest X-rays. Those presenting abnormal shadow on the initial X-ray received posteroanterior position chest X-ray. Those with suspected lesions according to chest X-ray findings were asked to provide two consecutive sputum samples for thick smear or concentrated smear and tubercle bacillus examination.

Survey findings: The national morbidity for active TB was 717/100,000, and the estimated number of patients was 6,900,000. Smear-positive morbidity was 187/100,000, and estimated number of patients was 1,800,000. The prevalence among children under 15 years was 0.853 % and was higher in urban areas than in rural areas. The identified active patients accounted for 35.7 %, and the identified smear-positive patients accounted for 55.8 %. Active patients receiving initial treatment and retreatment accounted for 73.3 % and 26.7 %, respectively. The smear-positive patients receiving initial treatment and retreatment accounted for 54.4 % and 45.6 %, respectively. Of all survey sites, 32.2 % never carried out BCG inoculation. (Ministry of Health of the People's Republic of China 1981).

This was the first time that China carried out nationwide TB epidemiological sampling surveys in the 29 provinces, autonomous regions, and municipalities, according to the standard survey plan, protocol, and implementation rules, which provided baseline data on the national and provincial TB epidemic (Ministry of Health of the People's Republic of China 1981). Based on the findings of this epidemiological survey, China designed its first 10-year TB Control Program. Another important outcome of this epidemiological survey was the establishment of a TB registration and reporting system in China. In 1984, China established its initial standardized annual TB case reporting system, thus ending an era that lacked standard reporting systems and unavailability of national data.

31.1.2 Second Nationwide TB Epidemiological Survey (1984–1985)

To evaluate the effectiveness of the TB response efforts since 1979 and observe the nationwide TB prevalence trend, in 1984 the MoH decided to launch the second nationwide TB epidemiological sampling survey. Twenty two provinces/autonomous regions/municipalities participated in the survey and, due to funding

constraints, seven provinces/autonomous regions/municipalities did not participate. The sampling methods were the same as those in 1979, with 749 survey sites. The scope of surveys was expanded over that in 1979, adding a TB mortality retrospective survey, sputum *Mycobacterium tuberculosis* culture, species identification, BCG inoculation history, and scar examination.

Survey findings: National morbidity for active pulmonary tuberculosis (PTB) was 550/100,000 and the estimated number of patients was 5,700,000. Smear-positive morbidity was 156/100,000, and the estimated number of patients was 1,620,000. Annual prevalence among children was 0.6 % in 1984 and 0.55 % in 1985, with a 6.28 % drop compared to that in 1979. TB mortality was 35/100,000, and PTB mortality was 31/100,000. The identified active patients accounted for 39.6 %, and identified smear-positive patients accounted for 56.4 %. Only 11.9 % of the known smear-positive patients were registered and treated at TB dispensaries. Among the 749 epidemiological survey sites, 78.5 % had carried out BCG inoculation (Ministry of Health of the People's Republic of China 1988).

Compared with 1979, the annual reduction rate of morbidity was 4.7 % for active PTB cases and 3.2 % for smear-positive PTB cases, achieving initial progress. Nevertheless, the TB epidemic was still serious despite the progress. Nearly 90 % of source patients did not receive standard treatment and management, and 21.5 % of areas did not implement BCG inoculation (Ministry of Health of the People's Republic of China 1988).

31.1.3 Third Nationwide TB Epidemiological Survey in 1990

To evaluate the implementation and effectiveness of the National TB Control Program in all provinces/autonomous regions/municipalities and provide scientific evidence for the development of the National TB Control Program (1991–2000), the MoH decided to conduct the third nationwide TB epidemiological sampling survey in 1990. The design, scope, and methodology of the survey were broadly consistent with those in the previous two surveys. The stratified cluster random sampling method was still used. There were a total of 928 survey sites across the country. The survey for the first time covered the TB sociodemographic situations and infection from nontuberculous mycobacteria (NTM).

Survey findings: The national morbidity was 523/100,000 for PTB and 134/100,000 for smear-positive PTB. It was estimated that there were 5.93 million active PTB cases across the country, including 1.51 million smear-positive PTB cases. The mortality was 21/100,000 for TB and 19/100,000 for PTB; TB deaths ranked seventh among the various causes for death. The annual TB prevalence was 0.97 %, with an annual reduction rate of 0.97 % in comparison with the epidemiological survey in 1979. The NTM infection prevalence was 15.4 %. The majority of patients (65.9 %) did not seek timely treatment following the onset of symptoms, and only 25.7 % of confirmed patients were registered and received treatment and management. All survey sites implemented BCG inoculation (Ministry of Health of the People's Republic of China 1992).

31.1.4 Fourth Nationwide TB Epidemiological Survey (2000)

To evaluate the implementation and effectiveness of the National TB Control Program (1991–2000), the MoH decided to conduct the fourth nationwide TB epidemiological sampling survey. This survey focused on TB epidemiological indicators and evaluation data. There were a total of 257 epidemiological survey sites. The design, scope, and methodology of this survey were broadly consistent with those in the 1984–1985 survey, with the addition of drug susceptibility testing (DST) for *M. tuberculosis*. Specifically, each subject with abnormal chest X-ray results or suspected PTB symptoms provided three sputum specimens for smear microscopy and culture. Specimens with positive results in sputum culture were further examined for strain identification and DST.

Survey findings: The morbidity was 367/100,000 for PTB and 122/100,000 for smear-positive PTB. It was estimated that there were 4.5 million active PTB cases across the country, including 1.5 million smear-positive cases. The annual TB prevalence was 0.72 %. The TB mortality was 9.8/100,000, with an average age of 55.2 years. The PTB mortality was 8.8/100,000. Known patients accounted for 32.8 % of all active PTB patients. According to the findings of the sociodemographic survey, 77.9 % of patients had an average per capita household income lower than the local annual per capita income. Of the PTB patients, 85.8 % had symptoms, of which 57.2 % sought treatment. The multidrug-resistant (MDR) TB rate was 10.7 %; the initial treatment MDR-TB rate was 7.6 %, and the acquired MDR-TB rate was 17.1 %. NTM cases accounted for 11.1 % (Ministry of Health of the People's Republic of China 2003).

From 1992 to 1999, China leveraged loans from the World Bank to implement the *China TB Control Program* in 13 provinces/autonomous regions (including Xinjiang), and leveraged central special funds to implement the *MoH Program for Strengthening and Promoting TB Control* in 15 provinces/autonomous regions (including Henan). As indicated by the findings of this epidemiological survey, the morbidity in program areas was lower than that in nonprogram areas, demonstrating the effects of programs. The programs directly contributed to the implementation of DOTS, management of PTB patients by the designated institutions, and treatment supervision in the new 10-year National TB Control Program (2001–2010). The policy of charge reduction and exemption started to be put into practice for PTB treatment: free treatment was provided to all infectious PTB patients incapable of paying relevant expenses.

31.1.5 Fifth National TB Epidemiological Survey in 2010

To look at the dynamics and harms of TB epidemic in different provinces across the country and evaluate the implementation of the National TB Control Program (2001–2010), the MoH decided to conduct the fifth nationwide TB epidemiological

sampling survey in 2010. This epidemiological survey focused on nationwide TB epidemiological indicators and evaluation data and adopted the stratified cluster proportional random sampling method. There were 176 national epidemiological surveys. Survey subjects were different from those in the previous four surveys. Specifically, survey subjects were permanent residents ≥15 years (i.e., their date of birth was before December 31, 1995). Chest X-ray was performed for all survey subjects. Three sputum smear examinations and two sputum culture examinations were performed for subjects with abnormal chest X-ray results or suspected PTB symptoms.

Survey findings: The national morbidity for active PTB in people ages 15 years or older was 459/100,000, 66/100,000 for smear-positive PTB and 119/100,000 for *M. tuberculosis*-positive PTB. It was estimated that there were 4.99 million active PTB cases, 720,000 smear-positive PTB cases, and 1.29 million *M. tuberculosis*-positive PTB cases among people over 15 years across the country. Compared with people age 15 years or older in 2000, the morbidity decreased by 1.1 % for active PTB, 60.9 % for smear-positive PTB and 44.9 % for *M. tuberculosis*-positive PTB, with an annual reduction rate of 0.1 %, 9.0 %, and 5.8 %, respectively. In eastern China, the morbidity was 291/100,000 for active PTB and 44/100,000 for smear-positive PTB. In central China, the morbidity was 463/100,000 for active PTB and 60/100,000 for smear-positive PTB. In western China, the morbidity was 695/100,000 for active PTB and 105/100,000 for smear-positive PTB, which was notably higher than in central and eastern China. The morbidity was 307/100,000 for active PTB and 49/100,000 for smear-positive PTB in urban areas, and 569/100,000 for active PTB and 78/100,000 for smear-positive PTB in rural areas. The morbidity was obviously higher in rural areas than in urban areas. Of the PTB patients, 43.0 % had no PTB symptoms, and 26.3 % of smear-positive patients had no PTB symptoms. Over half (53.1 %) of symptomatic patients had never sought treatment. Of the known patients, 90.1 % received anti-TB treatment; of these, 58.3 % received standard treatment.

Although cases of active TB in people ages 15 years and older did not go down substantially from 2000 to 2010, the smear-positive rate did show a significant reduction, demonstrating the effectiveness of the National TB Control Program (2001–2010) and also reflecting the variance of morbidity in different areas and the increase in the number of asymptomatic patients. These findings will provide evidence for the development and improvement of the new 5-year TB response strategy.

See Table 31.1 for a brief introduction to the methods used in four epidemiological surveys in China.

China conducted a total of five nationwide TB epidemiological sampling surveys. The first three surveys were conducted in representative provincial sites and provided both provincial and nationwide TB epidemic data. The last two surveys were conducted in representative national sites due to the limited funding input, difficulty in organization, and inadequate human resources, though some provinces independently added survey sites to conduct provincial surveys. China has improved the design, scope, methodology, organization, and implementation of surveys, updated data analysis methods, and gained valuable information. The highly cost-efficient

Table 31.1 Survey methods used in four National Epidemiological Survey in China from 1979 to 2010

Item	1979	1990	2000	2010
Total population	960,979,560	1,133,682,501	1,214,980,875	1,314,476,400
Sampling method	Stratified disproportionate cluster random sampling	Stratified disproportionate cluster random sampling	Stratified proportionate cluster random sampling	Stratified proportionate cluster random sampling
Sampling proportion	0.540278	0.588194	1:3152	1: 4967
Number of survey sites	888	928	257	176
Average number of subjects per survey site	1507	820–2492	1628	1437
Actual number of survey subjects (×1000)	1300	1460	360	250
Examination methods	(1) For children aged 3 months to 15 years: TST; if TST positive, chest fluoroscope. If results abnormal: chest X-ray, sputum smear of two sputum specimens	(1) For children aged 3 months to 15 years: TST; if TST positive, chest fluoroscope. If results abnormal: chest X-ray, sputum smear, and culture of two sputum specimens	(1) For children aged 3 months to 15 years: TST; if TST positive, chest fluoroscope. If results abnormal or suspected PTB symptoms are present: chest X-ray, sputum smear, and culture of three sputum specimens	For subjects ≥15 years: chest X-ray. If no X-ray, results abnormal, and/or suspected PTB symptoms are present: sputum smear and culture of three sputum specimens
	(2) For subjects ≥15 years, chest fluoroscope. If results abnormal: chest X-ray, sputum smear of two sputum specimens	(2) For subjects ≥15 years, chest fluoroscope. If results abnormal: chest X-ray, sputum smear, and culture of two sputum specimens	(2) For subjects ≥15 years, chest fluoroscope. If results abnormal or suspected PTB symptoms present: chest X-ray, sputum smear, and culture of three sputum specimens	

(continued)

Table 31.1 (continued)

Item	1979	1990	2000	2010
Scope of survey	(1) PTB prevalence	(1) PTB prevalence	(1) PTB prevalence	(1) PTB prevalence
	(2) TB infection rate	(2) TB infection rate	(2) TB infection rate	(2) Species identification and drug resistance surveillance for wild *M. tuberculosis* strains
	(3) Implementation of several main response measures (i.e., case detection, treatment, and BCG inoculation)	(3) TB mortality	(3) TB mortality	(3) Evaluation of TB response measures
		(4) Implementation of response measures (i.e., case detection, treatment and management, and drug resistance monitoring)	(4) Implementation of response measures (case detection, treatment and management, BCG inoculation)	(4) Social and economic status of PTB patients
		(5) TB social survey	(5) Social and economic status of PTB patients	(5) Public awareness of TB
		(6) Atypical mycobacterial infection	(6) Mycobacterium drug resistance	
			(7) NTM infection and drug resistance	
Main indicators	(1) PTB prevalence and morbidity in provinces/ autonomous regions/ municipalities	(1) PTB prevalence, morbidity, and mortality in provinces/ autonomous regions/ municipalities	National PTB prevalence, morbidity, and mortality	National weighted PTB morbidity
	(2) National weighted morbidity	(2) National weighted morbidity		

Note: Since some provinces did not complete the survey process during the second nationwide TB epidemiological survey in 1984–1985, findings of this survey are not presented here. *BCG* bacille Calmette-Guérin, *NTM* nontuberculous mycobacteria, *PTB* pulmonary tuberculosis, *TST* tuberculin skin test

survey protocol (through which more than 95 % of surveyed subjects receive examinations), field work process, and data analysis methods in China can be informative for countries that have high TB burden and need to conduct TB morbidity surveys.

31.2 Estimation of TB Incidence in China

The Government of China committed itself to achieve a detection rate of 70 % for new smear-positive patients by 2005. In May 2004, Chinese TB experts and WHO experts discussed scientific methods to estimate the incidence of new smear-positive patients and evaluate the detection of new smear-positive patients. The team jointly analyzed TB incidence in China and methods for the estimation of TB burden, reviewed various methods for the estimation of TB incidence (Dye et al. 1999; Dye and Bassili 2008), evaluated TB epidemic data that could be used for incidence estimation in a comprehensive way (van der Werf and Borgdorff 2007), and identified specific methods for the estimation of TB incidence in China.

31.2.1 Estimation of TB Incidence by Using Different Methods

According to the relations between TB incidence, morbidity and mortality, etc. in addition to directly estimating the incidence based on the registration rate and prospective cohort study, the WHO recommended four methods for the estimation of TB incidence (WHO 2011):

$$\text{Incidence} = \frac{\text{Morbidity}}{\text{Duration of disease}}$$

$$\text{Incidence} = \frac{\text{Registration rate}}{\text{Rate of case detection}}$$

$$\text{Incidence} = \frac{\text{Rate of death}}{\text{Mortality}}$$

$$\text{Incidence} = \text{Annual risk of tuberculosis infection} \times \text{Styblo coefficient}$$

31.2.1.1 Base Data Available in China

- Based on the tuberculin-related findings of the national and provincial TB epidemiological sampling surveys in 1990 and the 2000 nationwide TB epidemiological sampling survey, the TB prevalence can be obtained; hence, the annual risk of tuberculosis infection (ARTI) can be calculated.

- The numbers of active, smear-positive, and *M. tuberculosis*-positive PTB morbidities are available according to the national and provincial TB epidemiological sampling surveys in 1990 and the 2000 nationwide TB epidemiological sampling survey.
- TB and PTB mortalities are available according to the 1990 and 2000 nationwide TB epidemiological sampling surveys.
- Findings of the 1990 and 2000 national epidemiological sampling surveys on the clinic attendance of PTB patients and health services are known.
- The registration of TB patients in different counties/cities/districts and different years, and the proportions of patients on initial treatment or retreatment are known.

31.2.1.2 Estimation of Incidence Based on Morbidity

The method requires reliable morbidity data obtained by using the same survey method, and accurate average disease duration. China conducted nationwide TB epidemiological sampling surveys in 1979, 1990, and 2000. These covered the date of incidence of smear-positive PTB patients and the dates of their clinic attendance, diagnosis, and treatment. The date of disease can be estimated, but the exact duration of disease of TB patients can hardly be obtained directly. Therefore, the method of estimating incidence according to morbidity and duration of disease has been abandoned.

31.2.1.3 Estimating Incidence Based on Patient Registration Rate

Since 1992, DOTS has been implemented in 13 provinces through the China TB control project supported by the World Bank loan (the Health V Project; China Tuberculosis Control Collaboration 2004). In the areas where the National TB Control Program (NTP) and the DOTS have been implemented for many years, the registration rates of PTB patients are generally well maintained, and the surveillance systems are reliable. In the provinces covered by the Health V Project, the medians of patient registration rates in one quarter of the counties of each prefecture/city are calculated as the patient registration rates in the prefecture/city. Then, supposing the case detection rates in the counties are 60 %, 70 %, or 80 %, respectively, the incidence will be 42/100,000, 48/100,000, and 57/100,000. This method can be applied as an attempt to estimate the incidence or to verify the incidence data obtained based on the annual prevalence.

31.2.1.4 Estimation of Incidence According to Mortality

According to the WHO estimate, in 2000 the TB mortality in China was 19 %; according to the report for the 2000 nationwide TB epidemiological sampling retrospective survey, the national TB mortality in 1999 was 9.8/100,000, which may be attributed to the small number of death cases identified in epidemiological surveys,

a high case fatality rate estimation by the WHO, or both. The sample sizes of the epidemiological surveys are designed to achieve high representativeness and precision of the morbidity, not mortality, and sample sizes for the mortality survey were small. As the mortality survey was a retrospective survey, the patients' causes of death were mostly presumed and therefore the accuracy could be a problem (Yang et al. 2006). Estimating the incidence based on mortality is unreliable, and therefore this method has been abandoned.

31.2.1.5 Predicting Smear-Positive Incidence Based on Annual Risk of Infection

By referring to the available epidemiological survey findings and other surveillance data in China, experts reviewed and tried multiple estimation methods (WHO Regional Office for Southeast Asia 2006) and finally decided that the annual risk of infection is the appropriate basis for estimating TB incidence in China. Nevertheless, this method may unavoidably give unreliable results, and therefore needs other methods for verification.

The procedure for estimating the adjusted smear-positive incidence is as follows:

(a) According to the tuberculin survey findings in 1990, it is estimated that the annual risk of infection of children aged 0–14 was around 1 %, which is equal to the annual risk of infection of children born in 1983.
(b) Along with the development of the TB response in China, TB incidence has been dropping slowly. Suppose the ratio between smear-positive incidence and annual risk of infection is within the range of 50–60, the smear-positive incidence in 1983 can be within 50–60/100,000.
(c) According to the epidemiological survey findings, the smear-positive PTB morbidity in 1990 was 134/100,000 (with the range of 120–148/100,000). The smear-positive PTB morbidity was 110/100,000 in 2000 (while referring to the same diagnosis standard applied in 1990) with the range of 98–123/100,000. On such basis, it can be estimated that the annual reduction rate of smear-positive PTB morbidity was around 2 % from 1990 to 2000. Assuming the TB incidence reduction rate is less than the morbidity reduction rate, the incidence annual reduction rate should be within the range of 0–2 %.
(d) From 1990 to 2000, TB morbidity annual reduction rate was consistent with the annual risk of infection, i.e., within the range of 1.0–1.5 %.

Based on the above assumptions, the Styblo coefficient (Styblo 1985) was used to estimate the smear-positive PTB incidences in 2000, 2003, and 2005. Latin hypercube sampling (Palisade @*Risk* software) was used to evaluate the reliability of estimates.

Without any consideration of interactions between HIV and TB, the estimated smear-positive incidence was:

- 2000: 46.9/100,000 (90 % CI, 36–56/100,000)
- 2003: 45.7/100,000 (90 % CI, 34–56/100,000)
- 2005: 44.9/100,000 (90 % CI, 33–55/100,000)

According to the prediction of adult HIV prevalence by UNAIDS, the WHO estimated that the incidence of HIV/TB co-infection was 0.45/100,000 in China. The final incidences were calculated by adding this figure with the above estimates for different years. Special attention should be paid to the incidence of HIV/TB co-infection (especially when more and more TB patients test HIV positive) with further efforts to adjust incidence estimates in a timely fashion.

Assuming that the total population was 1.3 billion in China in 2003, it was estimated that there were about 601,880 new smear-positive TB patients. Based on the above steps, it was estimated that the total population was 1.32 billion in China in 2005, and there were about 599,650 new smear-positive PTB patients. Assuming that the annual growth rate of 1 % for the total population was balanced out by the annual reduction rate of 1 % for the TB incidence, the annual number of new smear-positive PTB patients would maintain unchanged in China in the upcoming years.

31.2.2 Prospect of Research on TB Incidence in China

The estimation of incidence can assist in developing TB control programs and objectives, making budgets, and evaluating the reliability of case detection rate via the ratio between the actual number of patients and the estimated number of patients. Currently, China is still exploring more appropriate incidence estimation methods.

Since 2004, China has established a sound web-based infectious disease reporting system which provides an important information platform for the evaluation of TB incidence. This system covers all health facilities in the country and has significantly improved the timeliness and integrity of PTB case reporting. In the future, efforts will be made to explore how to use the number of PTB patients from this system to reflect the actual number of patients. In addition, there are several cohort studies on TB incidence in China. These cohort studies may be combined with the web-based infectious disease reporting system to produce more accurate incidence estimates.

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Chapter 32
A Case Study: Japan—Evolution of Tuberculosis Surveillance in an Intermediate-Burden Nation

Toru Mori

32.1 Long-Term Trends of Tuberculosis Epidemics in Modern Japan

The tuberculosis (TB) epidemic of Japan reached its highest levels at the beginning of the twentieth century and has been characterized by four basic epidemiological trends. The first trend was initiated around 1911 with the historical first slow decline in the mortality rate and lasted until some years after the end of World War II (around 1948), with interruptions due to the influenza pandemic and the wars, each having produced temporary excess mortality. This trend was followed by a short but steep declining trend from 1948 to 1955 that may have been brought about by the elimination of war-related hardship and the effect of monotherapy of streptomycin that was first imported into Japan and later came to be produced domestically. The third trend is characterized by a considerably steep decline that lasted until around 1980 and is considered to have been enabled by the use of modern TB control measures and also by the favorable socioeconomic conditions (Mori 1995). After 1980, the drastic change in the age structure (brought about by the longer life of the elderly generations combined with lower birth rates) resulted in a slowing down of the incidence rate as well as of the mortality due to TB that is still continuing (Mori 2000).

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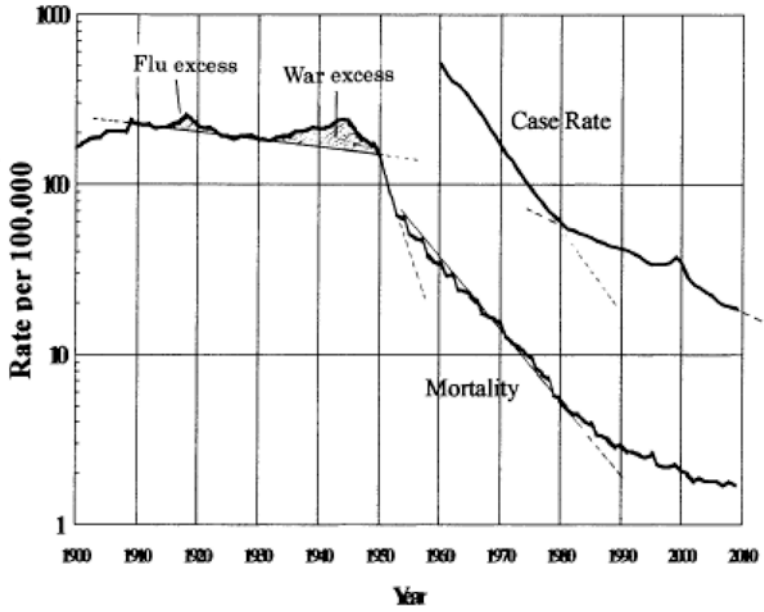

Fig. 32.1 Long-term trends of TB mortality and case rate, Japan, 1900–2009 (Mori 1995, 2000)

32.1.1 Earlier TB Epidemics and the Flu Pandemic

In pre-war Japan, the high prevalence of TB was the most serious health problem. According to the vital statistics, TB mortality was on the rise until the end of the nineteenth century (Mori 1995). When the industrial revolution was in progress, the TB epidemic spread first in the factories in the cities (mainly in the textile industry) and then to villages, and thus came to cover the whole country.

The epidemic reached its peak around 1910 and then started to decline slowly at a rate of about 1 % per year. This favorable trend is considered to be a consequence of the industrial revolution accompanied by the improvement of living condition, as seen in the western countries in the nineteenth century. This was the first breakthrough, or transition, in the TB epidemiology of modern Japan, one that constituted the basic trend in mortality for the next 40 years. This trend was interrupted, however, by the world pandemic of influenza of 1917–1918, which led to a tremendous rise in TB mortality, reaching a historical record rate of 257 per 100,000 in 1918 (Mori 1995). During 1917–1920, this caused an excessive number of TB deaths (estimated as the difference between TB deaths observed and those expected if the slow decline had continued from 1910) amounting to 57,000 (Fig. 32.1).

32.1.2 The Second Industrial Revolution and World War II

After 1920, the previous slowly declining trend resumed. However, this was again interrupted by a societal change, this time involving militarism after the mid-1930s. After 1935, the mortality curve departed from the trend established in the 1920s and took an upward trend. In 1941, when the Pacific War started, mortality started to rise acutely. Because there are no official vital statistics for the years 1944 through 1946, the rates for these years are estimated based on extrapolation of age-specific rates from both sides of the period. The rate is estimated to have reached 241 in 1944, then declined to 237 in 1945 and 208 in 1946 (all numbers per 100,000 population; Mori unpublished data). TB ranked number one among causes of deaths from 1935 through the end of World War II and accounted for more than 10 % of all deaths in this period (Mori 1995).

After the war, the curve was again restored to the baseline level by around 1948, as projected from the trend from 1920 through 1930. It has been estimated, in the same way as for the excess deaths due to the 1917–1918 influenza pandemic, that social hardship during the war claimed a toll of 480,000 more TB deaths than predicted by the baseline curve (Mori 1995; Fig. 32.1).

32.1.3 Changes After the War

A steep decline in TB mortality started soon after 1945 and is thought to have been initiated by the removal of the war-related factors causing excessive deaths. The impetus of this decline continued even beyond 1948, when the baseline level that had started in 1911 was recovered (Mori 1995). This may be due to the fact that war hardship had claimed too many deaths through 1948, leaving the less vulnerable part of the population to survive, thus resulting in a reactionary drop in mortality during the following years. Shortly afterwards, this drop was succeeded by the acute life-saving effect of chemotherapy, which was used first on a small scale and then on a massive scale after 1951 under the newly enacted TB Prevention Law (Mori 2000). The speed of the decline in mortality from 1948 through 1955 was as high as 20 % per year (Mori 1995). This represents the second transition of TB mortality in Japan.

After 1955, the mortality curve followed a slightly slower decline, which lasted another 25 years (Mori 1995). This third transition was brought about and sustained by an improved standard of living and intensive implementation of TB control measures. This transition was unique to Japan, as compared to many Western industrial countries where TB mortality had decreased well before the advent of modern TB control measures.

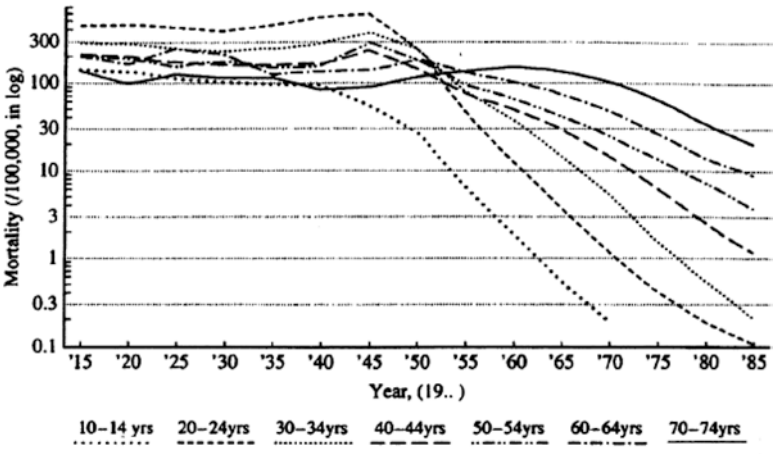

Fig. 32.2 Trends of age-specific TB mortality, Japan, 1915–1985 (Mori 1995)

32.1.4 Closer Analyses of the Changes Around the End of the War

Trends in mortality for different age groups are shown in Fig. 32.2. The excess in the mortality trend during the war can be seen among young people, but not among children and old people. Also, it is not remarkable among females in adolescence, and not clear for all ages. In passing, we note that the TB mortality was higher for females than for males until the early 1930s for all age groups combined. After 1935, this was reversed, and male predominance became more apparent after the war (Mori 1995).

For the younger age groups, a very steep and straight decline begins in 1945. In contrast, for the middle- and old-age groups, the decline is generally less steep, and for those aged 70 years or older, the decline starts as late as in the 1960s. Figure 32.3 presents age-specific mortality curves for different times of life. Before 1940, there is a peak of mortality among young age groups, with this peak shifting toward older ages from 1955 through 1975. Finally, mortality monotonically increases along with age (Mori 1995).

32.1.5 New Trends in Incidence Rates After the 1960s

After the introduction of a new TB registration system under the new TB Prevention Law in 1951 (see Sect. 32.3.2), a modern case definition (further modified in 1999) was established (Yamaguchi 1955). The mortality rate, whose value had become too small and imprecise, was replaced by the incidence rate (i.e., the case rate based on

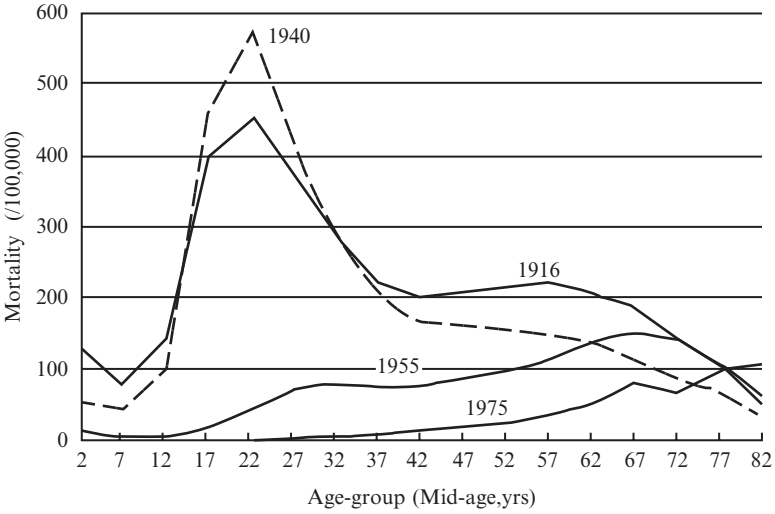

Fig. 32.3 Age-specific TB mortality pattern for different calendar years, all forms of TB, Japan, 1916–1975 (Mori 1995)

this definition) as a basic epidemiological parameter. The incidence rate has been decreasing by 11 % per year since 1961. However, the speed of the decline slowed toward the end of the 1970s, to about 3 % annually from 1979 to 1996. This trend reversed after 1996, with the rate increasing over that of the preceding year for three consecutive years from 1997 to 1999 (Mori 2000). The downward trend was resumed after 2000, returning to the previous slow speed of decline.

The slowing of the trend during the 1970s and 1980s was caused primarily by the aging of the population, i.e., by growth in the elderly age segment. The proportion of those aged 65 years or older among the Japanese population increased from 6 % in 1960 to 12 % in 1990 (Mori 2000). These age groups are the generations that had been heavily infected with TB in their youth, which leads consequently to an increase in the case rate of the entire population. The high case rate in the elderly is primarily due to their high prevalence of TB infection, but this is aggravated by various underlying conditions predisposing this group to TB, such as diabetes and other immuno-compromising conditions related to aging. In addition, the increase in elderly people developing TB increases the number of infection sources, which in turn causes infection and disease among the younger generations. When the age-specific trends in incidence rates are observed (Fig. 32.4), the curves for 60 and 70 years trend constantly downward after 1980, though less steeply, while those for the younger age groups exhibit a clear slowdown around 1980. In parallel with this, the incidence rate of smear-positive TB for all ages remained almost constant between 1970 and 1990, meaning that there was no reduction in sources of infection during this period (Mori 2000).

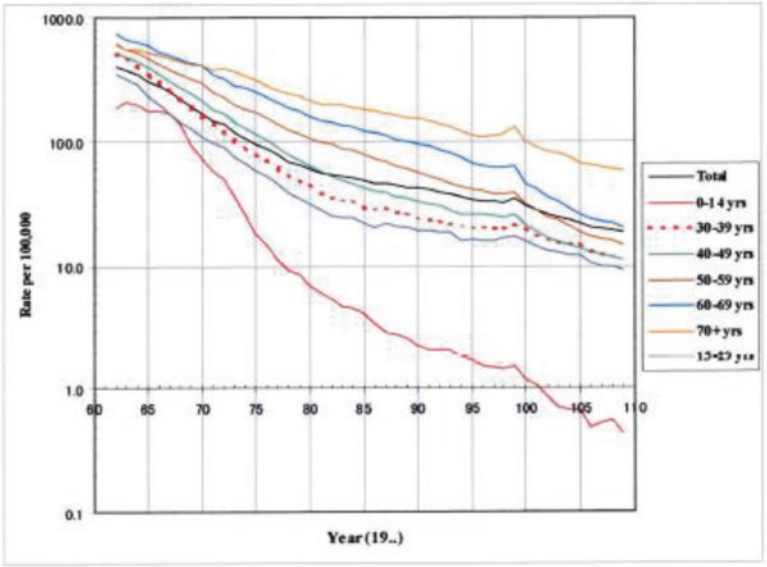

Fig. 32.4 Trends of age-specific TB case rates, all forms of TB, Japan, 1962–2009 (Mori 1995, 2000)

32.2 TB Trends Based on Risk of TB Infection

Styblo (1985) proposed that the annual risk of infection, i.e., the probability of an uninfected person being infected with TB within a year, is the optimum index of TB epidemiology. Then, Styblo et al. (1969) reported the example of the Netherlands (representing low-prevalence countries) with detailed analyses of the estimated risk and its trend, as well as the estimated and predicted age-specific prevalence of infection at various times. Japan has abundant data from tuberculin surveys to use as bases for calculating the risk of infection from the routine tuberculin testing among school children repeated every year after the war, but the information is of limited use because the data are all from bacille Calmette-Guérin (BCG)-vaccinated subjects. This is also true for tuberculin survey data from nationwide prevalence surveys conducted from 1953 to 1978 (Yamaguchi 1955).

The solution was brought about by data from a survey done in the Okinawa area. Okinawa, in the southernmost sea area of Japan, was retained under US administration after the war for strategic reasons. The public health services of Okinawa, including TB control, were under the strong influence of the USA. TB control, including clinical services, was the responsibility of seven health centers. Until 1967, as in the USA mainland, mass BCG vaccinations were not practiced.

In 1968, a TB prevalence survey was conducted concurrently with a survey taken on the Japanese mainland (Yamaguchi 1955). This survey included a tuberculin survey for all sample subjects who were almost free of a BCG vaccination history,

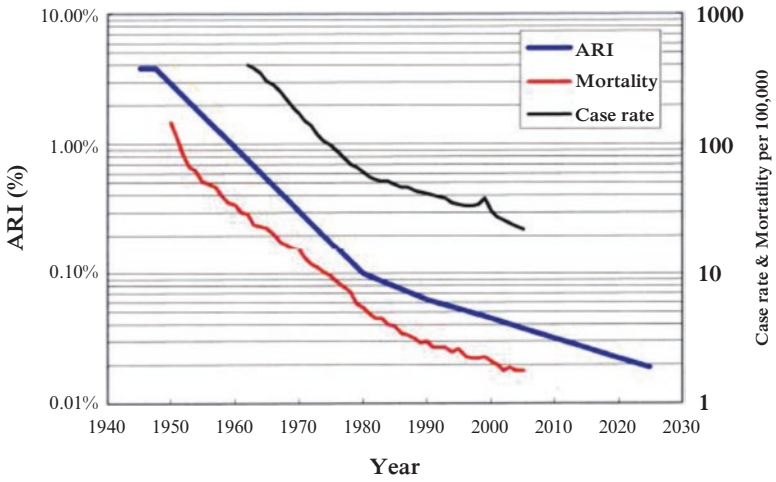

Fig. 32.5 Comparison of selected epidemiological parameters, Japan (Mori 2000)

except for students in junior high school who had been vaccinated just 1 year before at the school. In schools, BCG vaccinations were given only to tuberculin-negative subjects as tested before the vaccination. Thus, assuming that these BCG-vaccinated schoolchildren were not infected, it was possible to obtain the age-specific prevalence of TB infection. This enables estimating the level of annual risk of TB infection, as well as its trend over time, using Styblo's model (Mori 1971). Similar results were obtained from the next survey, conducted in 1973 (Department of Health and Welfare and Okinawa Prefecture 1973).

The level and trends of TB incidence and mortality were not very different from those of the Japanese mainland, and therefore it was considered realistic to assume that the known situation of TB infection in Okinawa represented that of the mainland (Fig. 32.5). This is also supported by the parallel trends of incidence and mortality on the mainland with respect to the estimated annual risk of infection. Also, the back-predicted prevalence of age-specific infections for 1950 agreed well with the actual tuberculin survey results for the downtown area of Tokyo obtained at the time (Japan Anti-Tuberculosis Association unpublished data).

Figure 32.6 presents the estimated age-specific prevalence of TB infection for 1950 and 2010, indicating the dramatic change in TB epidemiology in Japan during the last 60 years, going from a concave curve for 1950 with many adolescents being infected, to a sigmoid shape with the infected subjects concentrated in the elderly age groups (Yamaguchi 1955). TB infection information that originated from data taken in one area of Japan serves as an important basis of TB epidemiology for the entire country, even now contributing to future predictions and the monitoring of infection control.

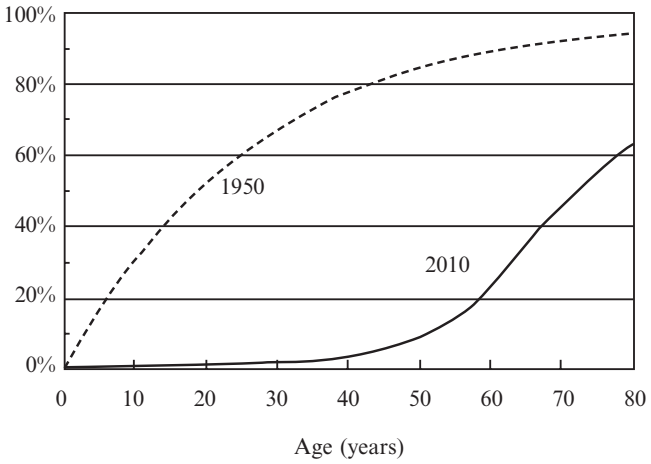

Fig. 32.6 Age-specific prevalence of infection (estimated) Japan, 1950 and 2010 (based on Mori 1971)

32.3 National Efforts for TB Control and the Establishment of a Surveillance System

TB control became a significant political issue for the Japanese government for the purposes of securing a productive workforce and maintaining a strong military power. The strengthening of TB control was one of the important motivations for the Japanese government to establish the Ministry of Health and Welfare, separate from the Ministry of the Interior, in 1938. In 1939, the Japan Anti-Tuberculosis Association was founded and patronized by the Royal Family in order to support the government's effort on behalf of the people (Japan Anti-Tuberculosis Association 1984).

The Association had outpatient clinics; sanatoria; and a Research Institute engaged in research on TB control and clinical technologies as well as the training of physicians, nurses, and technicians. Japan enthusiastically adopted development efforts such as BCG vaccination and early case-finding with mass miniature radiophotography.

32.3.1 The Dawn of Modern TB Control: BCG and MMR

The BCG vaccine was brought from France in 1924 and was used on a small scale in many places across the country. In 1942, it began to be given to the graduates of primary school, and in 1948 mass vaccination was introduced for everybody under the age of 30 years. An effort was made to improve the manufacturing technique of

the vaccine. In 1949, the freeze-drying method was completed and replaced the previously used liquid formulation (Japan Anti-Tuberculosis Association 1984).

In 1936, radiophotography was developed by Dr. Yoshihiko Koga (Japan Anti-Tuberculosis Association 1984) (independently developed in Brazil by Dr. Mauel Dias de Abreu at the same time; Hijjar et al. 2007) and began to be used in military camps and in several high schools. After the war, it was more widely used in the form of mass miniature radiophotography (MMR) services in schools, offices, and communities. A mobile unit (i.e., a bus with an X-ray system) running in towns and villages was a popular symbol of TB prevention in those days.

32.3.2 The TB Prevention Law and the Patient Registration System

After the introduction of chemotherapy, new legislation for TB control was enacted in 1951 in order to strengthen the fight against TB as a national policy (Yamaguchi 1955; Japan Anti-Tuberculosis Association 1984). The domestic manufacture of streptomycin had started in the previous year. The new law was intended to allow the drugs to be used widely for all patients, irrespective of their economic conditions. As was discovered soon afterward, there were millions of TB patients in need of treatment, while there were only a limited number of doctors with expertise in TB. Therefore, the government decided that all the doctors in hospitals and clinics should be recruited for administering TB treatment under the newly enacted TB Prevention Law. When a doctor diagnosed a TB patient, he/she was mandated to report it to a public health center (HC). The doctor then received a government subsidy for TB treatment using the regimen recommended by HC according to the national standards. In this way, all patients could receive hospital treatment as well as outpatient services free of charge or at a very low cost. This is what is currently called a "public-private mix" (WHO 2007). The HC was responsible for the support of patients and their families in order to ensure the continuation of quality treatment. These public health activities were performed under the TB registration system, and information obtained from this system became an important source for monitoring disease occurrences and for evaluating control activities. At the end of every year, annual reports of the registered cases were collected from the HCs and compiled into several cross-tables, and a summary of these tables was prepared and published for the nation and the prefectures.

When the incidence of TB resurged in the late 1990s, the Ministry of Health and Welfare announced a TB Emergency, calling for serious attention by the related institutions (Mori 2000). The government conducted a critical review of the national TB program (NTP), then abolished the TB Prevention Law and integrated the TB control program into the Infectious Diseases Control Law (Nakatani et al. 2002). Under the new legislation, priority was placed on treatment and contact actions, with less emphasis on traditional measures such as vaccination and MMR.

32.3.3 Nationwide TB Prevalence Survey

The first nationwide TB prevalence survey was conducted in 1953 in order to determine how well the national TB program responded to the problems and needs of the country (Yamaguchi 1955). This was a scientifically designed sampling survey (Styblo et al. 1969). The survey activities were implemented by the HCs, whose network had been expanded greatly after the war, as they played an important role in the control of TB and other infectious diseases as well as in mother and child health. A total of 51,011 subjects in 211 sample areas were interviewed and examined with chest X-rays, tuberculin skin tests, and bacteriology, achieving a remarkable completion rate of 99.3 %. The results were also alarming; the prevalence rate of active TB was 3.4 % for the entire population, including babies and the aged, amounting to about three million in absolute number, with half of these aged less than 30 years. It was also revealed that only 21 % of the survey-detected patients were aware that they had TB. Moreover, TB was determined to be prevalent in cities and villages alike. Based on these findings, the NTP was revised to strengthen MMR services and patient support, and there was an expansion of TB hospitals (Yamaguchi 1955).

32.3.4 Registry Information and Surveillance

The prevalence survey was repeated at 5-year intervals until 1973, and the results were incorporated in the revision of the NTP. In the later surveys, the sample size required to ensure precision grew larger because of the reduced prevalence rate, and it was not easy to achieve a high level of response rate in the survey (Shimao 1980). On the other hand, the proportion of survey-detected patients who were aware of TB (case-finding effectiveness) improved. Also, the registration system had been well managed so that information based on it could be considered reliable. Thus, the NTP decided to discontinue the prevalence survey and to depend on the registration information for identifying TB problems and monitoring the NTP.

According to this policy, a registry survey was conducted to determine the usefulness of the registration information and to characterize the present situation of the registered cases. In this survey, one tenth of the registered cases (active patients and inactive cases, i.e., cases under observation after completing treatment) were sampled at all of the HCs, and their records were collected and analyzed. The survey was conducted in 1978 and 1983, when 57,243 and 35,131 cases, respectively, were studied (Shimao 1980). These surveys confirmed that the registration information is useful enough to reliably and accurately detect problems in the process, from case-detection to treatment (e.g., treatment cohort analysis). Thus, it was decided to introduce a computer system to handle the registration services of HCs, which would be combined in a network covering each prefecture and ultimately the whole country. This computerized TB registry was launched in 1987.

32.3.5 Current TB Registry Information System

The public health center receives information on the patient's characteristics and the progress of treatment from the doctor seeing the patient from the notification report, the application for medical treatment subsidy, the hospital admission/discharge report, and other sources. This information is input to a computer database at the HC. The patients' records, other than ID information (name and address), are shared by the national and prefectural[1] surveillance centers through the internet. Each month, the national and prefectural surveillance centers prepare a monthly summary report covering the nation and its prefectures, or the prefecture and its health centers, in cross-tabulated form. Each year, after February, the registration information for patients notified during the preceding year is validated and errors are corrected if necessary (e.g., cancellation of cases whose diagnoses are judged as non-tuberculous) in preparation for the annual report. The annual reports from the national and prefectural surveillance centers include cross-tabulations of the characteristics of newly registered cases (e.g., age, sex, occupation, nationality, site of disease, method of case-detection, and underlying disease), the treatment outcome of the cohort of 2 years ago, and the status at the end of the year for active and inactive cases. The Research Institute of Tuberculosis[2] is responsible for analyzing the results, both cross-sectional (comparisons between regions) and longitudinal (trends), and publishing the findings. In many prefectures, the outputs of their own system are discussed by the local experts in the prefectural surveillance committee, with the results fed back to the HC or the medical community as an important basis for local TB programs (Fig. 32.7).

32.4 Perspectives into the Low Prevalence Situation

Japan's TB level still remains at that of an intermediate-burden nation, and it is not easy to overcome this. The most formidable epidemiological pressure is coming from the elderly population. The reduction of this level is largely dependent on the passing of this generation. The problem of other high-risk people is of a different nature. Socioeconomically marginalized or hard-to-reach people will emerge as a clear challenge to the TB control program. If this challenge is not taken seriously and managed well, Japan will suffer a critical resurgence of TB such as in the USA in late 1980s.

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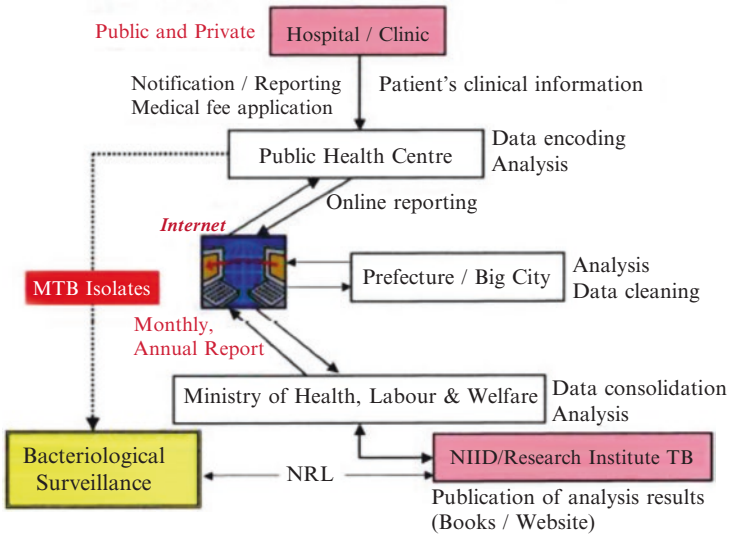
[1] Prefectures here include 47 regional and administrative divisions and about 20 large cities that have HC(s) under their jurisdiction.

[2] Research Institute of Tuberculosis (RIT) is an institution belonging to Japan Anti-Tuberculosis Association, a non-governmental organization setup in 1914. Though an NGO, RIT has been playing a role of the governmental organization by technically assisting the NTP, as well as implementing operational researches and training the NTP personnel.



MTB: Mycobacterium tuberculosis, NRL: National Reference Laboratory
NIID: National Institute of Infectious Diseases

Fig. 32.7 Computerized surveillance system of Japan, as of 2010 (Mori unpublished data)

In facing a trend such as this, we must strengthen patient support and thoroughly control the infection route more than ever. For these purposes, we should adapt a surveillance system that adequately addresses these challenges. Molecular epidemiological information must be integrated into the system to routinely deal with active infection tracking. We must also further refine patient support information management so as to enable sensible monitoring and evaluation of patient support. Attempts to develop a new surveillance system targeting these goals have started in some areas with high expectations of success.

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