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*Editors*

# Tuberculosis Control in Migrating Population

PEOPLE'S MEDICAL PUBLISHING HOUSE
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# Preface

With the rapid development of economy, international communication, tourism, migration, and labor, as well as world population mobility increase significantly. Such migration and mobility pose a serious challenge to the prevention and control of tuberculosis. Shenzhen, a new and open city in southern China near Hong Kong, has more than 10 million immigrants from all over China. Only a few cities in China and even in the world have such large population of immigrants. Large-scale population mobility makes tuberculosis epidemic control much more difficult. It can seriously endanger human health. We have carried out a systematic research on this important issue in human health for many years, constructed and implemented tuberculosis control strategy, initiated tuberculosis management and control model, and set up a tuberculosis control strategy for migrating population. Such strategy of monitoring system for tuberculosis control of migrating population in China has greatly reduced the epidemics of tuberculosis in the migrating population in Shenzhen; therefore, the incidence of tuberculosis has been effectively controlled. Such successful results have been well recognized by the WHO and the China Tuberculosis Control Organization.

In order to achieve the important WHO goal of "Eradicating Tuberculosis" by 2035, we need to make a marked progress in the discovery, registration, referrals, reception, and management of tuberculosis patients in migrating population. Additionally, it is of great importance to promote the strategy and measures for the advanced management and control of tuberculosis in the migrating population. Hence, we have organized data from more than 40 senior scholars who are actively in tuberculosis prevention and control and clinical research, including experts in prevention and control, infectious diseases, pulmonary, imaging, pathology, and experimental research. We also compiled the latest research results in tuberculosis prevention and control from China and abroad and composed a book entitled "*Tuberculosis Control in migrating population.*" The book is divided into ten chapters covering the epidemic of tuberculosis in migrating population, the strategies and technologies for control of tuberculosis, the diagnosis and treatment of tuberculosis, the management of tuberculosis in migrating population, and the prevention and control of tuberculosis in schools. We also present a new technology of emergency treatment during public health emergency, prevention and control of drug-resistant tuberculosis, double infection of TB/HIV, and so on. During the course of writing this book, we tried to keep track of the latest developments in the TB control in migrating population, prevention and treatment of drug-resistant tuberculosis, and HIV-associated tuberculosis.

This book is the first one in China and abroad focusing on prevention and control of tuberculosis among migrating population. This book provides comprehensive introduction and elaboration of prevention and control strategies, as well as integrates various research results. We compiled this book in such a way that it contains abundant content, several outstanding points, the lush pictures, strong practicability, and unique characteristic. It is a valuable book for medical workers and medical students in tuberculosis prevention and control, respiratory and infectious disease control, imaging department, laboratory, pathology

department, and other medical workers. At the same time, it is intended to provide a useful reference for the relevant medical workers in the world, especially in the "*the Belt and Road*" countries and regions.

Shenzhen, China Wei-ye Yu
Shenzhen, China Pu-Xuan Lu
Shenzhen, China Wei-guo Tan
May 12, 2019

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# About the Editors

**Wei-ye Yu, MD, PhD** Appointments and Positions:

- Director of Shenzhen Center for Chronic Disease Control. Chief Physician, Professor
- Master Student Supervisor of Guangdong Medical University

Research Directions:

- Prevention, clinical treatment, and scientific research of tuberculosis (including extrapulmonary tuberculosis such as tuberculous meningitis, bone tuberculosis, and genitourinary tuberculosis)

Research Productions:

- Professor Yu has published more than 50 papers which are related to tuberculosis prevention, diagnosis, or treatment. As a co-editor-in-chief, he has published six medical monographs, among which the monograph entitled *Diagnostic Imaging of Emerging Infectious Diseases* was published by Springer. He has completed or is hosting lots of research projects, including the National Major Scientific and Technological Special Project during the Eleventh and Twelfth Five-Year Plan Period and the National Key Research and Development Plan Project. Furthermore, he has won seven awards, including the second prize of the Scientific and Technological Progress Award of the Chinese Anti-Tuberculosis Association in 2017, the second prize of the Scientific and Technological Progress of Shenzhen Municipality in 2014, the third prize of the Scientific and Technological Progress of Guangdong Province in 2013, the third Prize of the Scientific and Technological Progress Award of the Chinese Preventive Medicine Association in 2007, the third prize of the Scientific and Technological Progress Award of Guangdong Province in 2007, the third-class merit from the People's Government of Guangdong Province, and the third-class merit from the People's Government of Shenzhen Municipality.

Social Positions:

- Chairman of the Internet Technology Branch of the Chinese Anti-Tuberculosis Association, Executive Vice Chairman of the Grassroots Tuberculosis Infection Control Committee of the Chinese Anti-Tuberculosis Association Vice President of the Beijing Innovation Alliance on Tuberculosis Diagnosis and Treatment, Vice Chairman of the Guangdong Provincial Antituberculosis Association, Vice Chairman of the Guangdong Provincial Leprosy Prevention and Treatment Association, Chairman of the Tuberculosis Branch of the Shenzhen Medical Association Member of the Tuberculosis Branch of the Chinese Medical Association, Executive Director of Shenzhen Medical Doctor Association, Executive Director of Shenzhen Medical Association, Deputy editor-in-chief of the Electronic Journal of Emerging Infectious Disease.

**Pu-Xuan Lu** is a professor and graduate supervisor of Guangdong Medical University and director of Department of Radiology, Shenzhen Center for Chronic Disease Control.

His academic titles include:

- Chief editor of Electronic Journal of Emerging Infectious Disease.
- Deputy chair, Radiology of Infectious Disease group at radiology branch of Chinese Medical Society.
- Deputy chair, Radiology of Infectious Disease group at Chinese Radiology Society.
- Deputy chair, Radiology branch of Chinese Sexually Transmitted Disease and HIV/AIDS Society.
- Deputy chair, Beijing Diagnostic Imaging Technology Innovation Alliance.
- Deputy chair, Radiology branch of Provincial Health Management Society of Guangdong, China.
- Editorial Committee Member, Journal of Radiology of Infectious Disease.

His research fields include:

- Diagnostic imaging and differential diagnosis of emerging infectious diseases, such as SARS, MERS, AIDS, human-infected avian influenza, tuberculosis, hepatitis, and other infectious diseases as well as clinical and basic sciences of emerging infectious diseases.
- Professor Lu has edited or co-edited more than ten academic treaties. *Diagnostic Imaging of Emerging Infectious Diseases* has been published by Springer in Nov 2015, which obtained national key award for book output in May 2017 by the General Administration of News and Publishing, China. In the recent 5 years, Professor Lu has directed and finished 5 national and provincial as well as international

collaborative research projects. He has published more than 150 research papers, including SCI indexed 43 research papers. And he received 12 awards from Chinese Medical Society, Chinese Preventive Medicine Society, Guangdong provincial government, and Shenzhen city government.

**Wei-guo Tan, MD** is a chief physician graduated from Sun Yat-sen University of Medical Science and Beijing Tuberculosis and Pulmonary Tumor Research Center. Presently, he is the Vice president of Pulmonary Disease Control Institute in Shenzhen Center for Chronic Disease Control and Secretary general of frontline tuberculosis control committee of Anti-Tuberculosis Association of China. He has more than 20 years of experiences in tuberculosis diagnosis, treatment, and prevention; he is in charge of more than 10 scientific research projects and has published plenty of high rank scientific papers.

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# Overview of Tuberculosis

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## 1 Prevalence of Tuberculosis

### 1.1 Concept of Tuberculosis and Its Evolution

Tuberculosis (TB) is a chronic infectious disease caused by the infection of *Mycobacterium tuberculosis* (Mtb) which spreads via respiratory tract. Lungs are the most commonly infected human organ whose infection accounts for above 80% of tuberculosis. Therefore, TB is also known as pulmonary TB [1]. There had been a long history of TB before its pathogenesis, spreading routes, treatment, and prevention of TB have been elucidated.

According to literature records, the human being has fought against tuberculosis, a classic infectious disease, for more than 4000 years. Early in the seventh century BC, TB-like symptoms were recorded in Assyria. Due to insufficient knowledge about its etiology and mechanism of transmission, pandemics of TB occurred till the twentieth century [2].

During the Hippocratic period in the ancient Greek in the fifth century BC, TB (lately known as phthisis) was the most widely spread disease and it was always fatal. At that time, many scholars in medicine, including Hippocrates, believed that TB is a hereditary disease. However, Aristotle disagreed and he believed that TB is an infectious disease. But because no evidence demonstrated his opinions, Aristotle was referred to as an outcast for a long period of time.

In the following centuries, two distinct schools emerged in Europe with a geographic boundary concerning the etiology of TB. In the northern Europe, TB was believed as a hereditary disease, while in the southern Europe, it was believed as an infectious disease. The distinction was partially due to geographic distribution of TB. At that time, it was believed that the wide spread of TB was caused by nomadic activities of Indo-European herdsmen. It was then confirmed that its pathogen, Mtb, is derived from M. bovis and the speculation of hereditary disease was abolished.

In the year 1720, Benjamin Marten, a doctor from Britain, firstly proposed that TB is an infectious disease but it was not confirmed. At the beginning of the nineteenth century, pandemic of TB occurred due to well-matched population density and natural conditions. In 1816, Rene Theophile Hyacinthe Laennec, the inventor of stethoscope, firstly elucidated the pathogenesis of TB and many terms he proposed concerning clinical intrapulmonary and extrapulmonary lesions of TB have been currently applied in clinical practice. In 1839, Johann Lukas Schönlein, a German doctor, firstly nominated the disease as tuberculosis. In 1865, Jean-Antoine villemin confirmed that TB is communicable from infected cadaveric tissue. In 1882, Robert Koch demonstrated his discovery of Mtb. And he won the Nobel Prize for medicine in 1905 in recognition of his contribution to pathogenesis of TB. In the nineteenth and twentieth centuries, due to the improved hygienic condition and quarantine of the infected population, the incidence of TB gradually decreased year by year.

Although the pathogen of tuberculosis, Mtb, has been isolated in the end of the nineteenth century, it costs nearly 50 years to develop a feasible treatment regimen. From the year 1914–1944, Selman A. Waksman dedicated himself to a hypoxic chemical drug that is applicable to human and he finally discovered streptomycin. However, Mtb is a microorganism that is strongly adaptable to the environment. If only one medication is applied to treat TB, Mtb tends to produce resistance to it. That is why the modern standard anti-tuberculosis regimen is a quadruple medication whose application is intended to prevent drug resistance.

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In 1921, Bacille Calmette-Guerin (BCG) vaccine was first applied to human, which then gained widespread application in Europe. Along with the application of effective anti-tuberculosis medications, such as sodium aminosalicylate, isoniazid, and pyrazinamide, a new era of combined medications for tuberculosis began. In 1959, a trial conducted in a medical center in India demonstrated that the effects of medication for tuberculosis have no difference between outpatients and inpatients. And it was proposed in the study that directly observed treatment should be applied to assure regular medication treatment in outpatients with tuberculosis.

In 1982, in a campaign celebrating the 100th anniversary of Mtb discovery by Robert Koch, an anti-tuberculosis institution in Republic of Mali, Africa proposed to establish the world anti-tuberculosis day. The proposal was soon adopted by the council of the International Anti-tuberculosis Association. But the memorial activities were launched in local areas. Till the end of 1995, March 24th was established as the world anti-tuberculosis day by the World Health Organization (WHO). In 1996, an official document was issued in China by the former Ministry of Health to initiate activities on March 24th, the world anti-tuberculosis day, each year in response to the WHO.

## 1.2 WHO and Evolution of Strategies for Tuberculosis Control

After the World War II, to keep peace and promote cooperation in economic, social, and human rights development, multiple sovereign governments including France, China, Soviet Union, Britain, and the USA initiated the establishment of the United Nations in 1945. At the establishment of the United Nations, the presidents of multiple countries proposed the establishment of a global health organization. And the World Health Organization (WHO) was finally established on April 7th, 1948. Since then, WHO has made joint efforts worldwide in fight for the infectious diseases such as influenza and HIV/AIDS as well as non-infectious diseases such as cancer and heart diseases.

In the 1960s and 1970s of the twentieth century, the short-term treatment for tuberculosis achieved success due to successive discoveries of effective anti-tuberculosis drugs. Since then, the treatment evolved into the directly observed treatment, short-course (DOTS) and has been gradually standardized. The standard DOTS has then been successfully applied in some countries of Africa, Asia, and Europe. At the 44th World Health Assembly in 1991, the WHO was informed that many countries lost their control to epidemics of tuberculosis due to neglects of the threats of tuberculosis to human health. Therefore, in April 1993, the WHO declared red alert of tuberculosis worldwide and re-assessed the post-strategies for tuberculosis control. In 1994, a new framework for tuberculosis control was proposed [3]. In 1995, the WHO officially proposed the modern anti-tuberculosis strategy (DOTS strategy) including the framework for tuberculosis control and DOTS, which was then promoted worldwide.

Since 1997, the WHO has been issuing the World Tuberculosis Report each year. The report provides important reference for scholars and clinicians in their understandings about epidemics of tuberculosis worldwide as well as newly developed diagnostic techniques, treatment regimens, and management strategies [4].

Due to limitations by the coverage and accessibility of the DOTS strategy, infection of HIV/AIDS, smoking, insufficient health care resources, and non-standard treatment regimen, the effects of DOTS strategy on tuberculosis control have been gradually weakened. Targeting the limitations in implementing the DOTS strategy, the WHO initiated a new strategy for tuberculosis control worldwide in March 2006, the Stop TB strategy. Meanwhile, the WHO established the goals to greatly reduce the global TB burden, to realize the Millennium Development Goals (MDGs) of the United Nations, and to reduce the morbidity and mortality of TB by 50% in the year 2015 based on the data of 1990, and to eradicate TB in the year 2050 (with an incidence of TB being less than 10 per million). TB is hopefully no longer a threat to the public health in the year 2050, according to the WHO.

In the World Tuberculosis Report of 2014, the WHO proposed the global strategy for tuberculosis after the year 2015, namely the End TB strategy. The general goal of the End TB strategy is to terminate the epidemics of tuberculosis worldwide. The WHO also proposed that the mortality rate of tuberculosis reduces by 75% and 95% in 2025 and 2035, respectively; and the morbidity rate of tuberculosis reduces by 50% and 90% in 2025 and 2035, respectively, compared to the data of 2015. In the year 2035, hopefully, no family has catastrophic expense on TB, according to the report [5].

## 1.3 Prevalence of TB Worldwide

According to data released in the 2018 World Tuberculosis Report by the WHO [6], TB is one of the top 10 deadly diseases worldwide and is the main cause of death from infection of singular pathogen. Its mortality rate is higher than that of HIV/AIDS. It has been estimated that the new cases of TB were 10 million worldwide in the year 2017 and the incidence rate was 133 per 0.1 million. The patients included 5.8 million male patients, 3.2 million female patients, and 1 million children. The adult patients aged above 15 years accounted for 90%, and the cases of TB complicated by HIV/AIDS accounted for 9% with 72% in Africa. In the 10 million new cases of TB worldwide, two-thirds were from India, China, Indonesia, Philippines, Pakistan, and the other three countries. The total number of cases in 30 countries with high TB burden accounted for 87% of all the cases worldwide. The incidence rate of TB showed great variance in different countries. The incidence rate of TB in most high-

income countries is lower than 10 per 0.1 million, while the incidence rate of TB in the 30 countries with high TB burden ranged from 150 to 400 per 0.1 million. But the incidence rate of TB in some countries including Mozambique, Philippines, and South Africa was higher than 500 per 0.1 million. A longitudinal study for etiology of tuberculosis demonstrated that in 10.4 million patients with pulmonary TB in the year 2016, 1.9 million can be attributed to malnutrition, 1 million to compromised immunity induced by HIV/AIDS, and 0.8 million to smoking and diabetes [7]. In the year 2016, the cure rate of TB was 82% worldwide, which was lower than 83% in 2015 and 86% in 2013 [6].

According to a study in patients with TB receiving no intervention, within 10 years after definitive diagnosis of TB by sputum smear positive, death occurred in about 70% patients. During the same period of time, 20% patients of TB with sputum smear negative but sputum culture positive died [8]. It has been reported that [6] in the year 2017, about 1.3 million patients with TB but HIV negative died from TB worldwide, showing a decrease of 29% and 5% compared to the years of 2000 and 2015, respectively. And about 0.3 million patients with TB and HIV positive died from TB in the year 2017, showing a decrease of 44% and 20% compared to the years of 2000 and 2015, respectively. According to the report, the mortality rate (every 0.1 million population) of TB decreased by 42% from the year 2000 to 2017. During the 5 years from 2013 to 2017, the mortality rate of TB showed a sharpest decrease in Europe and South-east Asia by 11% and 4% yearly, respectively. The mortality rate of TB worldwide was about 17%, with a yearly decrease of 3%, while the yearly decrease of its incidence rate was only 2%. To achieve the goal of stop TB in the year 2020, the yearly decrease of its incidence rate should be 4–5% and the mortality rate should reach 10% in the year 2020.

According to the report, drug-resistant TB is still a threat to the human health. In the year 2017, the new cases of multidrug-resistant TB and rifampicin-resistant TB were 0.1607 million, being slightly higher than 0.1531 million in the year 2016, and about 47% cases of drug-resistant TB were from India (24%), China (13%), and Russia (10%). Meanwhile, about 0.23 million patients with multidrug-resistant TB or rifampicin-resistant TB died [6]. In the year 2017, about 3.5% initially treated patients with TB and 18% re-treated patients with TB were diagnosed with extensive drug-resistant TB worldwide. In terms of treatment, in the year 2017, about 0.1391 million patients with drug-resistant TB worldwide received treatment, showing an increase compared to 0.1297 in 2016. However, those receiving treatment only accounted for 25% of the estimated number of patients with drug-resistant TB [6]. Concerning the outcome of treatment, the cure rate of drug-resistant TB was only about 55% worldwide, which still remained a low level.

According to the report, most deaths of patients with TB can be avoided by early diagnosis and timely standard treatment. In the years from 2000 to 2016, the early diagnosis and standard treatment have saved about 53 million lives of patients with TB [9]. Although many patients with TB can be accurately diagnosed and cured, gaps exist in the diagnosis and treatment of TB. In most countries with high TB burden, poverty, HIV/AIDS, malnutrition, and tobacco play more extensive and profound role in the prevention and control of TB [7]. A report about 119 countries with middle and low income indicated that the investment for prevention and control of TB amounted to 6.9 billion US dollars in the year 2018, showing an increase of 0.6 billion and 3.6 billion US dollars compared to the years of 2016 and 2006, respectively. And the domestic financial outcome accounted for above 86% [6]. Although the investment for prevention and control of TB has successively increased for more than 10 years, there is still an about 2.3 billion US dollars shortfall in funding worldwide [6, 7]. To make up the shortfall, domestic financial funding should be increased for prevention and control of TB in the countries with middle income, international financial help for countries with low income is also necessary.

Currently, 7 countries including Ghana, Kenya, Burma, Philippines, Moldova, Timor-Leste, and Vietnam have completed survey for disease burden in families [7]. The surveys in Burma and Vietnam indicated that the patients with TB and their families are facing heavy economic burden, which is consistent with the data that the expenses on disease by patients themselves account more than 30% of all the health care cost. The data from the Global TB Drug Facility (GDF) indicated that each patient with common TB spends about 40 US dollars for 6-month medication treatment and each patient with drug-resistant TB spends far more than that for treatment [7].

According to the report, the diagnostic technology for TB showed barely any new development. Currently, 20 anti-tuberculosis drugs are in Stage I, II, or III clinical trials, including 11 newly combined drugs. According to the results of the Stage IIb clinical trial, Bedaquiline and Delamanid acquired approval or conditional approval by the supervision agency. In addition, multiple regimens of new combinations are still in Stage II or III clinical trials. In 2018, 12 candidate vaccines are in clinical trials, including 4 vaccines in the Stage I clinical trials, 6 in the Stage II clinical trials, and 2 in the Stage III clinical trials.

## 1.4 Prevalence of TB in China

China as the country with the second largest population is also the second largest country of patients with TB and one of the high TB burden countries. In China, the number of new cases ranks as one of the highest in statutory class A and B infectious diseases. To timely understand the prevalence of TB all over the country, five epidemiological sampling surveys for TB were conducted in 1979, 1984–1985, 1990,

2000, and 2010, which provide basic epidemiological data for infection status, morbidity and mortality, and geographic distribution of TB [10–14].

According to literature report, at the early stage after foundation of P. R. China, the epidemics of TB were serious due to low economic level, insufficient health-care resources, and poor environmental conditions. In the year 1949, the morbidity and mortality rates of TB were 1750 per 0.1 million and 200 per 0.1 million and TB constituted a serious threat to human health in China [15]. Along with the economic development and improvement of living conditions, the morbidity and mortality rates of TB decreased by 70% (523 per 0.1 million) and 90% (21 per 0.1 million) compared to the data of 1949, respectively. However, from the global perspective, TB is highly prevalent in China, with high morbidity rate, high mortality rate, high drug-resistance rate (initial drug-resistance rate of 28.1%), and a decrease of annual decline rate (2.8%) [15]. To control the epidemic of TB in China, the Ministry of Health adopted a series of measures to improve the national regulations for prevention and treatment of TB, to establish and improve the national network for prevention and treatment of TB, to increase the funding for prevention and treatment of TB after the year 1991, such as to initiate TB Control Program in the World Bank Loan and to reinforce TB control program. By the year 2000, the national morbidity rate, mortality rate, and initial drug-resistance rate of TB in China had decreased to 346 per 0.1 million, 9.8 per 0.1 million, and 18.6%, respectively. Compared to the data of 1990, the morbidity rate, mortality rate, and initial drug-resistance rate decreased by 33.8%, 53.1%, and 33.8%, respectively, with annual decline rates of 4.0%, 8.3%, and 4.0%, respectively [11, 16]. Although the national prevalence of TB in China sharply decreased, there was still low detection rate of TB non-standard treatment and management of TB [11]. According to the 5th national epidemiological sampling survey for TB in 2010, the mortality rate of TB was 3.7 per 0.1 million, showing a decrease of 62.2% and annual decline rate of 9.3% compared to the data of 2000. The morbidity rate of TB was 459 per 0.1 million and drug-resistance rate to detected 11 drugs was 42.1% [10]. Due to variance in statistic methods and detected drugs, the morbidity rate and drug-resistance rate of TB in 2010 cannot be directly compared to the data of 2000. The results of survey indicated that the prevalence of TB in China was characterized by decreasing morbidity rate, increasing new cases, aggravating drug resistance, great regional variance in prevalence of TB, and increased percentage of asymptomatic TB cases [10].

China is also one of the high burden countries with drug-resistant TB. According to the data from the national baseline survey for drug-resistant TB in 2007–2008, the drug-resistance rate in initially treated patients with TB was 5.8% (175/3037) and the multidrug-resistance rate of re-treated patients with TB reached 25.3% (226/892). Compared to the data from the national epidemiological survey for TB in 2000, the epidemic of drug-resistant TB was aggravating [17, 18]. According to the data of the 2018 World Tuberculosis Report, the reported cases of drug-resistant TB in China were estimated to be 58,000, with the new cases of drug-resistant TB accounting for 7.1%. Currently, the cases of rifampicin-resistant TB were 108,000, with the new cases accounting for 12% and the re-treated cases accounting for 69% [6]. Compared to the data in 2017, the number of reported cases of drug-resistant TB remained the same and the number of reported cases of rifampicin-resistant TB decreased by 10,000. The epidemic of drug-resistant TB in China is severe. For Chinese governments, it is necessary to reinforce works in control of TB epidemics, including detection of drug-resistant and multidrug-resistant TB, construction of service system for prevention and treatment of TB, management of treatment and financial investment [19, 20].

## 2 Current TB Control

Pulmonary TB is one of the major infectious diseases, which is an old and serious threat to human health. During the 12th Five-Year plan in China, the prevalence of TB generally tends to decrease, with obviously decreased morbidity and mortality. The goal of the 12th Five-Year plan was ultimately achieved. A total of 4.27 million cases of active pulmonary TB were detected and managed and the cure rate remained above 85% [21].

However, China remained a country with high TB burden. There are still challenges in the prevention and control of TB, including gradually aggravating prevalence of drug-resistant TB, gradually enlarging population with HIV/TB, incomplete mechanism and system for prevention and treatment of TB, severe prevalence of TB in the middle-west and rural areas, difficult detection and management of TB in the migrating population. These situations should be improved by reasonable strategies for prevention and control of TB during the 13th Five-Year plan in China.

### 2.1 Commitment of the Chinese Government Concerning the Eradication of TB

Currently, the general goal in the prevention and control of TB is to stop prevalence of TB in the world in the year 2035. Specifically, the number of deaths from TB and the number of new cases should be decreased by 95% and 90%, respectively, in the year 2035, compared to the data of 2015. And the specific goals in 2020, 2025, and 2030 have also been established. These goals can be achieved based on the

comprehensive patient-centered prevention and treatment of TB, strong policies as the supporting system, and reinforced research and innovation [22].

Stop TB strategy by the WHO is intended to achieve its first goal in the year 2020, namely the numbers of deaths from TB and the new cases should be decreased by 35% and 20%, respectively, in the year 2020, compared to the data of 2015. And the patients with TB and their families should no longer pay for the catastrophic expenses on the treatment of TB [23].

On November 16–17, 2017, the 1st global ministerial conference of the WHO was held in Moscow. The theme of the conference was to eradicate TB in the era of sustainable development: multi-sector joint response. And the conference was intended to accelerate the implementation of Stop TB strategy proposed by the WHO and to eliminate the discrepancies in health-care accessibility and MDR-TB crisis. The conference advocated domestic and international commitments, achievements, and responsibilities to achieve the goals of Stop TB proposed by the WHO and Sustainable Development proposed by the United Nations [24]. In the conference, the ministers signed the declaration in accelerating movements to stop TB.

To accelerate movements to stop TB, presidents of many countries participated in the first high-level meeting of the United Nations Assembly on tuberculosis in New York of the USA on September 26, 2018. Multisectors were called politically for promotion of movements to stop TB.

## 2.2 Completion of a New Service System for Prevention and Treatment of TB

It has been definitively required in the 12th Five-Year plan for tuberculosis control and the Management for Prevention and Treatment of Tuberculosis issued in 2013 that a three-level network for prevention and treatment of TB should be constructed, and a new service system with designated hospitals, basic health-care institutions, and disease control institutions should be constructed. The new service system for prevention and treatment of TB emphasizes distinct responsibilities of different institutions. In addition, the responsibility of diagnosis and treatment of TB is transferred from the disease control institutions to the designated hospitals. The new service system has adapted to the needs of current prevention and treatment of TB and is in accordance with its future sustainable development. Since the implementation of the 12th Five-Year plan for prevention and treatment of TB, the new service system has been continually enriched and reinforced. The survey of designated hospital for diagnosis and treatment of TB in China in 2015 indicated that there have been 1,600 designated hospitals for diagnosis and treatment of TB [25] and coordination between different institutions has been explored.

The new service system for prevention and treatment of TB is gradually establishing. However, excessive diagnostic examinations and anti-tuberculosis drug abuse in treatment may exist in the designated hospitals. In some remote areas, the designated hospitals for diagnosis and treatment of TB are poorly equipped and the new technologies for detection and diagnosis of TB cannot be applied. There are discrepancies concerning the service quality of diagnosis and treatment in different designated hospitals. And the clinicians earn low income in the designated hospitals for diagnosis and treatment of TB and are not highly motivated for clinical practice. Some working staffs in prevention and treatment of TB have low incomes but high risks of occupational exposure. In addition to unstable allowance, the professional team remains unstable, which increases the difficulty in preventing and treating TB.

## 2.3 Advancement of Modern Strategy for Control of TB

The modern strategy for control of TB is centered on the control of infection source. In more than one decade with 100% coverage of DOTS. There have been free charge policy and incentive policy. In the free charge policy, the patients are provided with free charge X-ray for once and sputum smear for three times, and the patients with active pulmonary TB are provided with free charge anti-tuberculosis drugs according to the national uniform treatment regimen. And in the incentive policy, the basic level health-care staffs are provided with sickness subsidy and management grants. Based on these policies, some detections are added for free of charge and subsidies for health-care staffs are increased by the local government of China. Based on these policies and measures, the compliance of the patients is improved and the community-based health-care staffs are highly motivated for their clinical practice. Therefore, TB control is improved.

In China, patients finding is performed via multiple routes. Surveillance and screening of TB are performed in the high-risk populations, including the migrating population, students and teachers in schools, patients with type II diabetes, the senior citizens, patients with HIV/AIDS, custodial population, welfare population, and patients with drug-resistant TB. Gao et al. summarized the screening and control of TB in the high-risk populations [26]. They believed that the control of TB in the high-risk populations would be further emphasized along with increased government attention, increased financial funding, active social participation, and reform of health care institutions.

Combined with the technology of internet plus, DOTS can be reinforced and its effects can be improved by medication video, electronic medication kit, and other new technologies. Home isolation treatment can also be performed. Along with

the application of new technologies, information technologies, and mass data in diagnosis and treatment of TB, we can achieve the planning goals under the strong leadership of government and efforts of anti-tuberculosis professionals.

## 3 Development in the Diagnosis of Pulmonary Tuberculosis

Pulmonary tuberculosis, as an infectious disease, poses serious threat to human health. In the middle of the nineteenth century, Pasteur, a French scientist, established the theory of communicable pathogenic microbiology. Thereafter, the European scholars in medicine began to recognize that tuberculosis is communicable. In 1865, Villemin discovered that the clinical specimens from patients with TB can infect rabbits and other animals. And then the discoveries of leprosy bacillus and other pathogenic bacteria as well as developments in staining technology and coagulated serum medium promoted the development of pathogenic bacteriology. On March 24, 1882, Robert Koch, a German scientist, published a historic report, which revealed that the pathogen of tuberculosis is *Mycobacterium tuberculosis*. The discovery about pathogen of TB marked the birth of bacteriology of tuberculosis. Koch contributed to identification of Mtb as the pathogen of TB, microscopy of glass slide for Mtb and plate culture, which constituted the basis for the bacteriological diagnosis and identification of TB. Based on the bacteriological diagnosis and identification of TB, immunology and modern clinical therapeutics of TB were developed. Till today, the well-known three principles in identifying pathogenic bacteria developed by Koch have been observed in identification of pathogenic bacteria. The discovery by Koch provoked people's expectation to avoid sufferings of TB. And scholarly studies soon focused on the Mtb itself, diagnosis and treatment of TB, and Mtb vaccines, with emergence of a research climax on TB. Koch and his contemporaries developed many concepts and technologies, which are now valuable legacies of medicine. And many basic bacteriological methods and bacteriological diagnosis have been applied till today.

TB is caused by infection of Mtb. Currently, there has been no effective vaccine to control the infection of Mtb. Treatment of patients with TB is the key point in the strategy of TB control. It has been generally believed that detection of Mtb is the basis for the definitive diagnosis of TB [27]. Therefore, the bacteriological diagnosis of TB is the beginning of TB control and the responsibility of the laboratory of tuberculosis bacteriology is to detect Mtb in the specimens of the patients. Routine smear microscopy and culture in TB bacteriology are the classical techniques when our ancestors discovered Mtb in the end of the nineteenth century, which have been effective nowadays. However, the techniques have their own defects, which render that bacteriology of tuberculosis remains to be the most important research field for clinical practice of tuberculosis. It has been expected that the clinical bacteriological diagnosis of TB should be rapid, specific, sensitive, accurate, and simple with low cost that adapts to clinical laboratories. However, research for almost 100 years has not achieved breakthrough developments. And the recent development in molecular diagnosis brings a ray of hope for an ideal technology in bacteriological diagnosis of TB [28].

### 3.1 Bacteriological Examination

#### Smear Detection

Acid-fastness is a physical property of certain bacteria, specifically their resistance to decolorization by acids during laboratory staining procedures. Once stained as part of a sample, these organisms can resist the acid and/or ethanol-based decolorization procedures common in many staining protocols. The acid-fastness of genus Mycobacteria is due to the high mycolic acid content of their cell walls, which is responsible for the staining pattern of poor absorption followed by high retention [29]. In addition, Corynebacteria and Nocardia may also be partially acid-fast due to their content of mycolic acid. Based on the knowledge, we know that acid-fastness is not specifically Mycobacteria but a possible preliminary implication. Therefore, when rod shaped bacteria with acid-fastness is detected in a clinical specimen, acid-fast bacillus positive rather than Mtb positive should be reported. In clinical practice, acid-fast bacillus is considered to be equal to Mtb as indicators in the diagnosis of TB [30–32].

#### Culture Detection

Mtb is facultative bacteria which is aerobic and has no complex requirement for nourishment. It can grow in test tubes at appropriate temperature. Compared to smear for microscopy, culture detection is more sensitive and shows positive for sputum specimen with a concentration of 100 bacteria/ml. After isolation culture, the *Mycobacterium tuberculosis* complex (MTBC) and *Mycobacterium tuberculosis* strain can be identified and drug sensitivity can be tested. Culture detection can provide bacteriological basis for Mtb infection [33].

#### Nucleic Acid Amplification

Since the polymerase chain reaction (PCR) was developed in the year 1983, the new technology of gene diagnosis with advantages of rapidity, high sensitivity, and high specificity has been expected to open up a new era for the diagnosis of TB [34]. PCR is an in vitro enzyme driven amplification of specific sequence segment in the nucleic acid of Mtb medicated by a pair of specific oligonucleotide primers. The target

sequence specific to Mtb is denatured, renatured, and elongated in a series of 20–30 repeated thermal cycles and the sequence is exponentially amplified for detection. High standards of technology and reagents are required in performing PCR. Clinical observations have demonstrated that PCR has a high false positive rate in clinical diagnosis. And many scholars attempted to improve the technique for its clinical application, such as nested PCR and PCR plus nucleic acid probe [35]. Growth independence is the advantage of nucleic acid amplification but the source of detected target sequence cannot be determined from living or dead bacteria. Therefore, its application in the diagnosis of TB is limited.

Bacteriological examination plays an important role in the diagnosis of TB and the definitive diagnosis of TB mainly depends on culture positive, which is also the golden standard for other laboratory diagnostic methods. Currently, routine bacteriological diagnosis for TB is not satisfying. Smear for microscopy is simple with low cost, but it shows low sensitivity and no strain specificity. And its specificity is decreasing along with increasing cases of non-Mtb infection. Although culture for detection is highly sensitive, the report is sometimes delayed and it always fails to detect the growth-heterotypic Mtb.

The technique of molecular diagnosis is highly sensitive, but with a high false positive rate. However, it provides the most rapid and accurate preliminary diagnosis of TB and we should take the full advantage of it. Recently, the drug-resistant gene of Mtb can be rapidly detected by using techniques of molecular biology such as PCR-SSCP and sequence analysis, including rpoB gene mutation of Mtb strain that is resistant to rifampicin, kaG, inhA, and aphC genes mutation that is resistant to isoniazid, kasA gene mutation, pncA gene mutation that is resistant to pyrazinamide, mps and ms genes mutation that is resistant to streptomycin, rs gene mutation that is resistant to amikacin/kanamycin, embCAB gene mutation that is resistant to ethambutol, and gyrA and gyrB genes mutation that is resistant to quinolones as well as IrA gene mutation that inhibits coding of transcription proteins. In addition, it has been reported that resistance to clarithromycin by Mtb is possibly related to rs gene mutation; resistance to ethionamide, inhA gene mutation; and resistance to seromycin, urA/dadB genes mutation. These discoveries marked the advancements in the molecular biology of TB [36].

## 3.2 Imaging Diagnosis of Pulmonary TB

### Chest High Voltage Photography

Chest high voltage photography is chest photography with an electric voltage of no less than 120 kV. It is characterized by short wave length of X-ray with strong penetrating power, low dosage of X-ray absorption by tissues, decreased density discrepancies of different tissues, decreased covering effect on the films, increased data, and enhanced image readability. The increase of electric voltage correspondingly decreases the electric current, which greatly reduces damages to human body and enhances the clarity of images. The advantages of chest high voltage photography include (1) increased data on films with decreased density of soft tissues and ribs and decreased covering effect; (2) clear demonstration of lesions adjacent to mediastinum and posterior to the cardiac shadow; (3) demonstration of internal structures of the lesions, such as calcification and cavity.

### Computed Tomography (CT)

Computed tomography is abbreviated as CT. With the development of technology, CT has developed into current spiral CT and ultrahigh speed (electron beam) CT. And its scanning mode has developed from translation plus rotation and rotation plus rotation into static plus rotation, namely slip ring and spiral scan. The number of detector in CT scanner has been increasing and their arrangement has developed from continuous dense type into multilayer type, namely multilayer spiral CT scanner. The scanning time has been shortened from 3–5 min to 0.2–1 s. CT scan is characterized by clear demonstration of transverse sections of human body, high resolution power, clear demonstration of TB lesions at different stages, and accurate demonstration of hilar and mediastinal lymphadenectasis. In addition, modern computers are empowered with powerful image post-processing technology, such as multilayer reconstruction and virtual endoscopic reconstruction. In addition to harvest of clear images of transverse sections by thin layer scanning, virtual 3-dimentional images can be synthesized. CT has been an important imaging technique in the diagnosis of pulmonary TB and it has outweighed chest X-ray photography.

### Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) was firstly developed by scholars from the USA, Bloch and Purcell. In 1978, Damadian firstly applied the technology in clinical practice and named it as MRI. The underlying mechanism is proton resonance of hydrogen atom. Hydrogen atom is the substance in human body with the largest number, containing only one proton that is the most unstable. Under the effect of external magnetic field, resonance of proton can be produced. That is to say, the protons in hydrogen atoms in human body are arranged disorderly with different directions of magnetic moments. When these self-spinning and disorderly protons are placed in a powerful and homogeneous external magnetic field, they are re-arranged along with the magnetic lines of force of the external magnetic field. At this time, when triggered by radio-frequency pulse from a specific second magnetic field, the hydrogen nuclei absorb the energy to produce resonance. Because hydrogen atoms are widely

distributed in human body, the hydrogen protons are used as probes and transmitter-receivers to collect MRI signals and their distribution within human body. In MRI, human body is placed in a powerful and homogeneous magnetic field and the protons in hydrogen atoms are magnetized for directional arrangement. A specific radio-frequency is in processional motion around the magnetic field. The radio-frequency pulse with the same frequency as the proton processional motion is applied to trigger and deflect the magnetic moment of proton. And the self-spinning protons leave the planes of magnetic field to produce resonance at a certain frequency. When the electromagnetic wave is cut off, the self-spinning of protons in resonance gradually recovers to the original low energy thermal equilibrium, namely relaxation. At this time, the hydrogen nuclei radiate electromagnetic wave with the same frequency, which is known as resonant electromagnetic wave. The resonant electromagnetic wave is received for spatial coding in a computer to determine the spatial distribution of detected nuclei. A converter is then applied to reconstruct image for its display on a monitor, which is known as the image of MRI. By MRI, the substance with short T1 long T2 signal produces strong self-spinning echo wave of MRI signal, while the substance with long T1 short T2 signal produces weak signal due to low signal of flowing void effect. MRI is non-invasive and is capable of harvesting 3-dimensional image of any plane in human body. In addition, it can demonstrate cardiac chambers and vascular lumen with no application of reagent and facilitate differentiation of benign and malignant neoplasms based on T1 and T2 signals. Due to these advantages, it has gained wider application in clinical diagnosis.

## 3.3 B-mode Ultrasonography

B-mode ultrasonography is an important part of modern diagnostic imaging in clinical practice. Based on different penetration and reflection of ultrasound on different tissues and lesions, the images are constructed to accurately display the outlines, ranges, and properties of organs and lesions. The image by B-mode ultrasonography provides direct view of tissues and organs. It is non-invasive and provides dynamic observation with no radiation effects. Nowadays, it has been widely applied in the diagnosis of thoracic and abdominal diseases. Due to strong reflection of ultrasound to the gas containing lungs and interference of bone tissues in the thoracic wall, ultrasonography can hardly demonstrate micro-structures in deep lungs. Therefore, it is commonly believed that ultrasonography is not appropriate for the examination of thoracic cavity. However, many thoracic diseases can be demonstrated by ultrasonography such as fluid containing lesions, parenchymal lesions in lungs and atelectasis. In such cases, the lesions contact to the thoracic wall to form acoustic window, which increases the penetration of acoustic beam and clear ultrasound image can be harvested.

### Thoracic TB

B-mode ultrasonography demonstrates early thoracic TB as abscess of the thoracic wall that is no-echo or weak-echo dark area. The lesion is fusiform along the intercostal space that is internally and externally dumbbell shaped. In its advanced stage, when the abscess invades the bone, the bone lamella is irregularly thin with interrupted or absent echo from the bone cortex. The abscess cavity is demonstrated with irregular flakes or spots like strong echo and accompanying acoustic shadow. Prolonged ultrasonography demonstrates internal surface of thoracic wall with purulent dark area, which protrudes towards the lung field with irregular boundary. There is also irregular weak sinus echo.

### Tuberculous Pleurisy

In the cases of pleural effusion, the parietal and visceral pleura are separated and the space is demonstrated as fluid no-echo dark area. Encapsulated effusion is demonstrated as limited dark area with no echo or extremely weak echo. And the dark area is characterized by oblate in shape, medially protrusion towards the lung, and the two ends in sharp angle. The emergence of homogeneous light spot in the fluid dark area commonly indicates bloody effusion, while irregular and different sized light spots with uneven distribution indicate purulent effusion. In sitting position, liquid level dark area under strong gas echo or spots of gas strong echo in the liquid dark area are considered to be hydropneumothorax. B-mode ultrasonography has important clinical value in the diagnosis of pleural effusion, with a diagnostic accordance rate of above 98%. In the diagnosis of pleural effusion, it has the advantages in (1) detecting the location and quantity of pleural effusion; (2) qualifying thoracic shadow; (3) definitively diagnosing pleural effusion in the cases with a small quantity of effusion that is hardly demonstrated by chest X-ray; and (4) accurately and safely guiding puncture and drainage.

## 3.4 Fibrobronchoscopy

### Principles of Fibrobronchoscopy

In a fibrobronchoscope, tens of thousands fiberglass with favorable light conductivity are orderly arranged whose both ends are fixed with ethoxyline resin to form light transmitting bundle and image guide bundle. The diameter of single fiber for light transmission is 15–30 m, while the diameter of single fiber for image guide is 5–20 m. The key point for light transmission and image guide is com-

plete optical isolation of each fiberglass. That is to say, each fiberglass is coated with transparent substance with lower reflective index than the fiberglass to transmit light bundle along the fiberglass with no leakage. Therefore, the image from fibrobronchoscope is actually consisted of countless light spots. The fiberglass is subject to aging and rupture. When one fiberglass is broken, there is a black spot in the image guide bundle and thus the brightness of transmitted light is affected.

#### The Common Demonstrations of Bronchial TB by Fibrobronchoscopy

The mucosa of affected bronchus is demonstrated with congestion and edema. The interbronchial crest is widened and the cartilage rings are poorly defined. There is also bronchial lumen stenosis of different degrees.

On the mucosal surface of affected bronchus, there is erosion or singular/multiple ulcers, which may be covered by caseous substance or thick moss like secretions. The mucosal and submucosal congestion and edema are demonstrated around the ulcers.

The affected bronchus is demonstrated with mucosal and submucosal granuloma and accompanying luminal stenosis or obstruction. The lesions may be misdiagnosed as bronchogenic carcinoma.

Broncholymphatic fistula may be demonstrated and there are congestion and edema around the fistular orifice. When the patient coughs, caseous substances may be discharged from the fistular orifice. The old fistular orifice is demonstrated as small brownish depression.

The affected trachea and bronchus are demonstrated to be funnel shaped or even with occlusion due to obvious cicatricial stenosis. Meanwhile, the lesion may be complicated by irreversible atelectasis, which is commonly sequela of untreated or inappropriately treated serious tracheal or bronchial TB.

### 3.5 Serological Diagnosis

After years of studies on the serological diagnosis of TB, attempts have been made in the methodology, purified specific antigen, monoclonal antibody of the corresponding antigen, and recombinant antigen [37]. Serological diagnosis of TB is expected to provide valuable information on the diagnosis of Mtb negative TB, extrapulmonary TB, and pediatric TB. But the results are hardly satisfying. Multiple antigens have been defined in the serological diagnosis of TB, but the recombinant antigens have achieved unsatisfying results in the diagnosis of smear positive and smear negative TB [38–40]. And their clinical application is unpromising. Therefore, the serological diagnosis plays assistant role in the diagnosis of TB.

### 3.6 Detection of Cellular Immune Response

Anti-tuberculosis immunity is a T cell centered immune response participated by multiple immune cells. The activated T cells and macrophages play their roles in mediating immune responses via production of cytokines. The cytokines are a series of immune active factors with variant properties, sources, and effects, which form a highly efficient network. Based on the mechanism, the observation of cellular immune response and detection of cytokines, such as IFN-γ, TNF-a, II-2, II-4, I-12, and IL-10, in patients with suspected diagnosis of TB can provide significant data for the further diagnosis. And as the Th2T characteristic cytokine, IFN-γ has gained the most intensive scholarly attention in related scientific research [41, 42].

Generally speaking, bacteriological examination is the most reliable laboratory test for the diagnosis of TB. However, being the same as the other diagnostic techniques, bacteriological examination has its advantages and limitations. The clinicians should know well about the weight of each technique. Currently, the diagnosis of TB is still a comprehensive diagnosis based on the clinical face-to-face assessments. No laboratory test or diagnostic imaging can substitute the clinicians in diagnosing TB. Therefore, clinical experience plays important role in the diagnosis and treatment of TB.

## References


1. Wang, C. Screening for biological markers specific to pulmonary tuberculosis and identification of genes responsible for its susceptibility. Zhejiang University, 2016.
2. Niemi R. A brief history of Mycobacterium tuberculosis' Etiology. [2018-11-9]. http://www.intellectualventureslab.com/invent/brief-mtb-history.
3. He GX, Wang LX. Evolution of strategies for tuberculosis control. Forum Prev Med. 2008;14(6):481–4.
4. World Health Organization. Global tuberculosis control: surveillance, planning, financing: WHO report 2006. Geneva: World Health Organization; 2006.
5. World Health Organization. Drug-resistant TB: surveillance & response: supplement to the global tuberculosis report 2014. Geneva: World Health Organization; 2014.
6. World Health Organization. Global tuberculosis report 2018. Geneva: World Health Organization; 2018.
7. World Health Organization. Global tuberculosis report 2017. Geneva: World Health Organization; 2017.
8. Tiemersma EW, Van Der Werf MJ, Borgdorff MW, et al. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One. 2011;6(4):e17601.
9. World Health Organization. Tuberculosis: fact sheet. [2018-11-9]. http://www.who.int/mediacentre/factsheets/fs104/en/.
10. Wang LX, Cheng SM, Chen MT, et al. Report of the 5th national epidemiological sampling survey for tuberculosis in 2010. Chin J Anti-tuberc. 2012;8:485–508.
11. Technique Guidance Team of the National Epidemiological Sampling Survey for Tuberculosis. Report of the 4th national epidemiological sampling survey for tuberculosis. Chin J Tuberc Respir. 2002;1:6–10.

12. Duanmu HJ, Liu YX, Shi HS, et al. Data analysis of the 3rd national epidemiological sampling survey for tuberculosis. Dis Surv. 1995;7:215–7.
13. Leaders Team of the National Epidemiological Sampling Survey for Tuberculosis. Comprehensive brief of the national epidemiological sampling survey for tuberculosis in 1979. Chin J Anti-tuberc Commun. 1982;2:3–6.
14. Kan GQ, Zhang LX. Implications of the 2nd national epidemiological sampling survey for tuberculosis. Chin J Anti-tuberc Commun. 1989;3:97–101.
15. Song WH. Global emergency of tuberculosis and the control of TB in China. Chin J Epidemiol. 1997;18(2):109–11.
16. Liu YH, Jiang GL, Zhao LP, et al. The 4th national epidemiological sampling survey: analysis of drug resistance by Mycobacterium tuberculosis. Chin J Tuberc Respir. 2002;4:32–5.
17. Wang SF, Zhao B, Song YY, et al. The risk factors of drug resistant tuberculosis in China: data analysis of the national baseline survey for drug resistant tuberculosis in 2007. Chin J Anti-tuberc. 2013;4:221–6.
18. The Technique Guidance Team of the National Epidemiological Sampling Survey for Tuberculosis. Report of the national epidemiological sampling survey in 2000. Chin J Anti-tuberc. 2002;2:3–46.
19. Shen X, Song SC, Lei SG. Prevalence and control strategy for drug resistant tuberculosis. Occup Health. 2017;4:566–8.
20. Cheng SM. Current control of multidrug resistant tuberculosis and recommendations. Chin J Trop Med. 2017;3:213–5.
21. General Office of State Council, P. R. China. The national 13th five-year plan for prevention and treatment of tuberculosis. http://www.nhfpc.gov.cn/bgt/gwywj2/201702/7b2a362da2da4841a362f8eb36575b67.shtml.
22. Interpretation of the 2015 world tuberculosis report: evolution of control strategies for tuberculosis. http://www.chinatb.org/kxyj/gjkydt/201602/t20160223_125564.htm.
23. Implementing the End TB strategy: the essentials. http://www.who.int/tb/publications/2015/end_tb_essential.pdf?ua=1.
24. The First Global Ministerial Conference of World Health Organization. http://www.who.int/tb/endtb-sdg-ministerial-conference/zh/.
25. Li L, Liu YH, Ma Y, et al. Evolution of the service system for prevention and treatment of tuberculosis in China and its implications. Chin J Anti-tuberc. 2016;38(11):904–7.
26. Gao JH, Cen ZY, Tan YQ. Development in screening and control of tuberculosis in high-risk populations in China. J Youjiang Med. 2016;44(1):105–8.
27. National Anti-tuberculosis Association of China. Standard procedures in the bacteriological diagnosis of tuberculosis. Chin J Anti-tuberc. 1996;18:28–31.
28. Pan YX, Wu W. Molecular markers for bacteriological surveillance during treatment of tuberculosis. Chin J Tuberc Respir. 2001;24:393–5.
29. Chen XY. Research progress of tuberculosis diagnosis. Chin J Clin. 2013;41(3):11–4.
30. Zhang TM. Sub-clinical tuberculous sepsis. Chin J Tuberc Respir. 2001;24:622–4.
31. Mithison DA. The action of antituberculosis drug in short-course chemotherapy. Tubercle. 1985;66:219–25.
32. Van Grietnuysen AJ, JaMorgan MA, Horstmeier CD, et al. Comparison of a radiometric method (bactec) and conventional culture media for recovery of mycobacteria from smear-negative specimens. J Clin Microb. 1983;18:384–8.
33. Nsz AR, Buiting AGM. Comparison of fluorescent Bactec 9000MB system, Septi Check AFB system and LowersteinJensen medium for detection of mycobacteria. J Clin Microb. 1996;34:2391–4.
34. Chen XY, Wang HP, Jin YS, et al. Detection of Mycobacterium tuberculosis DNA by Taqman PCR and its clinical application. Chin J Tuberc Respir. 2000;23(5):284–8.
35. Han XQ, Ma Y, Gao WW, et al. Detection of drug resistant Mycobacterium tuberculosis by bacteriophage biological amplification, DNA sequence analysis and single-strand conformation polymorphism analysis. Chin J Tuberc Respir. 2004;27:815–9.
36. Hu ZY, Ni LD, Jin AJ, et al. Methodological study on rapid detection of Mycobacterium tuberculosis by bacteriophage biological amplification. Chin J Tuberc Respir. 2004;27:801–5.
37. Xie LMY, Gao WW, et al. Significance of interferon-γ release from mononuclear cells of peripheral blood after antigen stimulation in the diagnosis of Mycobacterium tuberculosis infection. Chin J Tuberc Respir. 2005;28:545–9.
38. Aubert-Pivert EM, Chedeverge FM, Lopez-Ramirez GM, et al. Cytokine transcripts in pediatric tuberculosis: a study with bronchoalveolar cells. Tuber Lung Dis. 2000;80:249–58.
39. Campos-Neto A, Rodrigues-Junior V, Pedral-Samparo DB, et al. Evaluation of DPPD, a single recombinant Mycobacterium tuberculosis protein as an alternative antigen for the Mantoux test. Tuberculosis. 2001;81(5-6):353–8.
40. David ST, Mukunkan U, Brahmadath KW, et al. Detecting mycobacterium for diagnosing tuberculosis. Indian J Med Res. 2004;119:259–66.
41. Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. Lancet. 2003;361:1168–73.
42. Houghton RL, Lodes M, Dillon DC, et al. Use of multiepitope polyproteins in serodiagnosis of active tuberculosis. Clin Diagn Lab Immunol. 2000;9:883–91.

# Epidemiology of Tuberculosis in Migrating Population

2

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## 1 Status Quo of the Migrating Population

### 1.1 Overview of the Migrating Population

So far, there has been no consistent scholarly definition for the migrating population. *Report of Population Migration in China across the Century and the migrating Population* issued by Population Institute, Renmin University of China defined the migrating population as population living in the county or subdistrict for more than 6 months with registered permanent residence at the same place or living in the county or subdistrict for no more than 6 months but not at the place with registered permanent residence for more than 6 months subtracting those the population with the registered permanent residence at the other county or subdistrict in the city [1]. The definition of migrating population emphasizes the registered permanent residence, period of time, and living place. The migrating population refers to the specific migrating population with changed living place but no corresponding change of the registered permanent residence. Therefore, the migrating population is technically the population with changed living place with no corresponding change of the registered permanent residence, namely population with separated living place and registered permanent residence with exceptions of those migrating populations for schooling, travelling, visiting relatives and friends, and participating in the military army. The migrating population is closely related to the policies of registered permanent residence. In a broad sense, the migrating population refers to those leaving the place of registered permanent residence and living in another place. And in a narrow sense, the migrating population refers to those migrating people spontaneously participating in socioeconomic activities to make a living with exceptions of those with a short-term stay at a place rather than their living place [2]. The occupations that the migrating population commonly engages in include manufacturing (such as architecture, factories, and mining industry), transporting, agriculture, forest industry, commercial, and service industry.

The policy of registered permanent residence in China renders co-existence of the migrating population and the population with changed registered permanent residence. And in most other countries, such distinction does not exist. Therefore, in the international scholarly society, some pairs of concepts are applied in the studies of population migration in China, such as permanent migration and temporary migration, migration with registered permanent residence, and migration with no registered permanent residence, official migration, and non-official migration. The latter terms of these three pairs of concepts are the migrating population. Population migration and non-permanent migration are not characteristic of China. Internationally, studies on circulation of population in developing countries are active. The studies revealed that circulation of population is a common phenomenon in developing countries that is commonly covered by routine data [3]. And the policy of registered permanent residence and its related policies are not the only reason for temporary living of the migrating population at a place with no registered permanent residence [4]. In the countries with no policy of registered permanent residence, the abilities of migrating population and their families as well as configuration strategy of family resource and interests between the places of influx and their original living place are factors limiting the circulation and migration of populations. In addition, innate fluctuation of labor market at the influx place due to the change of market needs, separation of the labor market between the capital intensive primary sectors and labor intensive secondary sectors, and the corresponding employment strategy of the enterprises are all factors influencing the migration and circulation of migrating population.

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## 1.2 Migration of Population in the Developed Countries

In the period of mid-nineteenth century to mid-twentieth century, the main developed countries experienced the process of rapid urbanization. There have been large-scale migrations of populations during the rapid industrialization and urbanization in these developed countries. And the direction of population migration was in consistent to the direction of industrial development and industrial agglomeration. In the 1980s of the twentieth century, about 2.5–3 million people worldwide migrated into another country and the tendency has been no signs of attenuation [4, 5].

In the migrating migrant workers of the USA, 74% visited clinics once or twice during the past 3 years, 22% never visited clinics, and 61% were deprived of health-care service by laws. However, the federal government has paid enough attention to the prevention and treatment of TB in the migrating migrant workers [6, 7]. A survey in the USA revealed that 20% of the 313 patients with active TB are illegal immigrant and 6% of the patients are afraid of troubles from the immigration office and dares not to see a doctor [7].

The migration population living in urban and rural areas of Australia has been increasing, which is partially because immigration plan was introduced and expanded in some states and regions by the Australian government. The immigration plan was in response to the comment on the living environments and societies of immigrants in rural and urban areas in Australia. The approximate data about size of immigration populations in urban and rural areas of Australia, labor force participation rate and unemployment rate of Australian born population, median of weekly income per person, and percentage of highly skilled occupation were released. The difference of education level in immigrants was the most significant, with the education level in urban immigrants far higher than that in other populations, especially university education. The gender difference in the immigrants was much higher than that in Australian born population. In recent years, the education level, occupational skills, and incomes of Australian immigrants showed significant increase.

## 1.3 Migration Populations in the Developing Countries of Africa and Latin America

Along with the reform of social and political policies in Africa, the imbalance of regional economic development has been aggravating and the allocation of productive force has been changed. The population has been migrating at an unprecedented speed in Africa, which, to a large extent, changed the spatial distribution of population in Africa. The migration of population in Africa is characterized by migration towards the economic zones, coastal areas as well as industrial and mining centers. The developments of industry, agriculture, and transportation in coastal areas give rise to more employment opportunities to the migrating population, which intensely attract the flow of inland population into the coastal areas. The flow of population is especially obvious in the western Africa. And the population rapidly flows into the copper mine areas, such as Zaire and Zambia, gold and diamond mine area of southern Africa, and oil patches in northern Africa and Nigeria. In addition, large rural population in Africa migrates into urban areas, which accelerates urbanization in Africa. With migration of large rural population into cities, many countries in Africa have been facing some serious socioeconomic and public health issues, such as shortage of housing, unemployment, traffic jams, environmental deterioration, insecurity, and insufficient health-care resources.

Based on insufficient industrialization in Latin America, migration of rural population into cities and the excessive concentration of population cause the phenomenon of over urbanization. An overview to Latin American indicated that the urban population increased by 45.2% in the 1950s of the twentieth century, 45% in 1960–1970, 43.6% in 1970–1980, and 40.3% in 1980–1990. The urban population has expanded to more than 0.3 billion in 1990 from 30 million in 1930 [8]. In the USA, the percentage of urban population increased from 30% to 70% within almost 100 years, while it reached the same percentage in Brazil within 40 years [9]. Over urbanization is also characterized by more rapid urbanization than industrialization. Although the urbanization in Latin America is driven by industrialization, the development of industrialization is far slower than the urbanization. The economic development lags far behind the migration of population and labors. Till mid of 1970s in the twentieth century, the urban population in Latin America accounted for 60% of the total population, while the industrial population accounted for less than 20–30% [10]. The lagging of industrialization behind the urbanization causes serious social problems, such as insufficient employment opportunities for rapid inflow of population and labors within a short period of time. Therefore, the population migrating into cities commonly lives in poverty due to unemployment or semi-employment. They cannot obtain stable income and social security. In addition to poverty and unemployment, over urbanization also causes urban environmental pollution, traffic jams, insecurity, and insufficient supplies of electricity and water. The incidence rates of poverty, drug abuse, robbery, and raping are comparatively high in slum areas. And the increasingly serious social problems, to some extent, negatively affect the development of urban and even national economy.