Epidemiology and control of multidrug-resistant tuberculosis in China
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SUMMARY

This thesis aimed to describe the epidemiology of multidrug-resistant tuberculosis (MDR-TB) in China in order to contribute to the development of a more effective MDR-TB control and prevention program. Specifically, it aimed to determine the prevalence of MDR-TB in China, identify patient-related risk factors for MDR-TB, determine the outcomes of MDR-TB after treatment completion with the standard regimen, identify health service related risk factors such as availability of appropriate drugs and use of inappropriate treatment regimens, and finally to assess infection control.

Chapter 1 provides a global overview of MDR-TB epidemiology, development, transmission, and risk factors as well as the MDR-TB situation in China. With over 9 million cases and nearly 2 million deaths annually, tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. Drug-resistant tuberculosis, especially MDR-TB presents a significant challenge for global TB control and has become a serious public health problem in many countries.

According to World Health Organization (WHO) estimates, China has the second largest number of TB cases in the world, with more than 1.3 million new cases of TB every year. Of the 37 reported communicable diseases in China, TB ranks the first in terms of number of cases and deaths. China also has a high prevalence of drug-resistant TB and ranks not only second among the 22 highest TB burden countries in the world but is also listed as one of the 27 highest MDR-TB burden countries. Based on a recent national anti-TB drug resistance survey it was estimated that 120,000 new MDR-TB cases emerge annually in China. (MDR) TB is a major public health problem in China.

The problem of drug-resistant TB is man-made. There are four main categories of risk factors for drug-resistant TB: health services related risk factors, patient behavior related risk factors, socio-demographic risk factors and epidemiological risk factors. Most risk factors are related to a poorly functioning national TB control program which, for example, may not properly implement the directly observed treatment short-course (DOTS) strategy - a TB control strategy developed by the WHO after TB was declared a global health emergency in 1993.
In the context of the new Stop TB Strategy, the follow-up of DOTS, a pilot program for programmatic management of drug-resistant TB at two different Global Fund TB Project sites in China was implemented in October 2006. By the end of July 2010, the programmatic management of the project covered 41 prefectures/cities in 12 provinces in which 14,609 MDR-TB suspects were screened, and 1,978 (13.5%) MDR-TB cases were identified. Among these MDR-TB cases, only 1,049 (53.0%) cases were treated with a standardized treatment regimen recommended by the WHO. To date, the Global Fund Model has achieved some progress in MDR-TB Control in China, and the MDR-TB control program is currently gradually being expanded.

Chapter 2 presents an overview of the results of the drug-resistance surveys conducted in ten provinces (representing 38% or 483 million out of 1.27 billion inhabitants of the total population in China) between 1996 and 2004, which indicated that MDR-TB levels varied greatly between provinces in China. Of 14,059 smear positive patients tested, 11,052 (79%) were new TB cases. The weighted mean prevalence of MDR-TB among all cases was 9.3% (5.4% among new cases and 25.6% among previously treated cases) and most MDR-TB patients were resistant to at least one other first line drug. Our study also showed that the MDR-TB rate in China was, on average, much higher than the global estimated average of 4.8%.

Chapter 3 investigates genotyping characteristics of and risk factors for MDR-TB and MDR-TB strain clustering in Shandong province, China. A case-control study was conducted to compare all 100 MDR-TB cases to a random selection of 97 pan-susceptible TB cases hospitalized at Shandong provincial TB hospital from April 2007 to July 2009. The study showed that a large proportion of MDR-TB cases in Shandong province were caused by recent transmission. We also found several factors significantly associated with MDR-TB cases in multivariate analysis, including previous TB treatment, history of TB symptoms for more than 3 months before the first visit to the TB hospital, and a lack of health insurance. Also MDR-TB was associated with lower socio-economic status and the Beijing genotype TB strain.

Chapter 4 reports the treatment outcomes of the 2004 cohort of MDR-TB patients who received treatment with standardized first line drug regimens as assessed in the second half of 2008, and evaluates conventional smear microscopy as a predictor of long-term prognosis. Our investigation showed the reported cure rate with standardized first
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Line drug regimens for MDR-TB patients in Heilongjiang province in China was 83% among new and 66% among retreatment patients based on smear microscopy - high values compared to what is observed in other countries. However, MDR-TB patients deemed to have been cured in fact had high recurrence and death rates within four years after treatment with standardized first line drug regimens. This provided evidence that conventional smear microscopy used to determine the treatment outcome for MDR-TB cases or the reporting and recording method/quality or both were flawed.

Chapter 5 assesses the availability of second line drugs and the use of drug susceptibility testing results for the treatment of TB in 4,675 health care facilities in 12 provinces. Second line drugs are widely available in China for the treatment of both TB and other diseases. However, only a fraction of the facilities which diagnose and treat (drug resistant) TB patients use drug susceptibility testing to guide their choice of treatment regimen. External quality assurance is rarely performed for culture and drug susceptibility testing, while for smear microscopy it is conducted in only about half of the facilities. Current practice regarding second line drug use was observed to be widely divergent from national policy, which prescribes standardized regimens that include only first line drugs for both new and retreatment patients. The type and level of health care facility were more important predictors of second line drug availability than whether or not they were part of the national TB control program (i.e. TB centers). In the locations where second line drugs were accessible for the treatment of MDR-TB, fewer than three classes of second line drugs were available in approximately a third of the facilities. Use of regimens with an insufficient number of effective drugs will facilitate creation of further resistance, potentially leading to extensively drug-resistant TB (XDR-TB).

Chapter 6 describes the various TB treatment regimens used in six different TB hospitals in China. This investigation showed that only 18% of patients with new cases and 9% of patients with retreatment cases were prescribed standard TB treatment regimens. This indicated that incorrect TB treatment regimens are prevalent in Chinese TB hospitals, heightening the risk for the development of drug resistant TB. Despite the fact that TB hospitals have better equipment and more well-trained medical staff than the TB centers, there is still a pervasive lack of adherence to accepted and established TB treatment protocols.
Chapter 7 assesses TB infection control practices in the TB centers and the prevalence of latent TB infection and TB disease among health care workers in Henan, the province with the largest population (97 million) in China and a high MDR-TB prevalence (12.9% in 2001). The assessment of infection control practices in Henan showed that the patient consultation areas and X-ray areas were separated from the waiting areas and administrative areas only in a small minority of the centers. Mechanical ventilation was not available in any of the TB centers. N95 respirators were not available for health care workers, and surgical masks were not available for TB patients and suspects in most TB centers. The latent tuberculosis infection (LTBI) prevalence of health care workers without a BCG scar was 49.0%. Older health care workers, health care workers with longer duration of employment, and health care workers who worked in departments with increased contact with TB patients had a higher prevalence of LTBI. Health care workers in TB centers at the prefecture level or with an inpatient ward also had a higher prevalence of LTBI. The prevalence of active TB disease was 6.7/1000 among medical staff, much higher than the prevalence (3.0/1000) among the general population. This suggests that TB infection control in TB centers in Henan was inadequate and the prevalence of LTBI and TB disease among health care workers was high.

Chapter 8 contains a general discussion of the key findings described in this thesis and addresses some of the methodological issues encountered in the different studies conducted. In this chapter we also discuss the challenges specifically associated with MDR-TB control in China, as well as how MDR-TB control and prevention can be improved. Finally, this chapter also provides several suggestions for future research. The main recommendations for TB control in China are that drug susceptibility testing should be rapidly extended to diagnosis MDR-TB among all bacteriologically confirmed TB cases. Current inappropriate usage of second line drugs should be prohibited and controlled by policy, and second line drug management and administration should be strictly based on drug susceptibility testing results. Full coverage of programmatic management of drug-resistant TB is urgently needed. Finally, TB infection control practices in health care facilities should be strengthened in China.