Epidemiology and control of multidrug-resistant tuberculosis in China

Xue He, G.

Citation for published version (APA):
Xue He, G. (2012). Epidemiology and control of multidrug-resistant tuberculosis in China.
CHAPTER 8
Drug-resistant tuberculosis (TB), especially multidrug-resistant tuberculosis (MDR-TB) presents a significant challenge for global TB control and has become a serious public health problem in many countries.\textsuperscript{1-4} According to World Health Organization (WHO) estimates,\textsuperscript{3,5} China is among the 22 highest TB burden countries in the world as well as one of the 27 highest MDR-TB burden countries.\textsuperscript{2,4} China accounts for 24\% of global MDR-TB cases.\textsuperscript{6} Although numerous reasons for the occurrence and proliferation of MDR-TB have been reported,\textsuperscript{7-19} the root causes of widespread MDR-TB in China are still not fully understood.\textsuperscript{20-22} This thesis aimed to contribute to and develop a better understanding of the epidemiology, transmission, and risk factors associated with MDR-TB in China, which is crucial for the country’s development of a more effective MDR-TB control and prevention program. In this chapter we discuss the current situation, risk factors and challenges associated with MDR-TB, as well as how to improve MDR-TB control and prevention in China.

**MDR-TB PREVALENCE, ASSOCIATED RISK FACTORS, AND OTHER ISSUES IN CHINA**

Before conducting any research on MDR-TB and its prevalence and associated risk factors in China, it is important to understand that China is a large country with drastically different regions. The characteristics exhibited in one area of the country may be completely different from those in another part. For example, Beijing, the capital of China and a special municipal region, is rapidly developing into a world-class city with many industrialized country amenities. However, this belies the fact that China is still a developing country and most of the country does not enjoy the level of development observed in China’s first-tier cities. It is to be expected that the stark differences in the level of development, education levels, incomes, and access to quality health care between regions are also reflected in the regional differences in TB incidence and proportions of drug-resistant TB. Indeed, the most obvious finding observed from drug resistance surveys conducted from 1996 to 2004 in ten different provinces covering 38\% (483 million out of 1.3 billion inhabitants) of the total Chinese population was that MDR-TB levels varied greatly between provinces in China (Chapter 2). The MDR-TB prevalence in China’s most affluent province, Beijing, was 3.5\% while the prevalence in some of the less developed provinces – Heilongjiang, Inner Mongolia, Henan, Liaoning – all ranged in the double digits with Liaoning having the highest prevalence at 23.3\%. The weighted mean prevalence of MDR-TB among all
provinces was 9.3%. Using this survey of 10 different provinces as an indicator of the current overall MDR-TB situation in China, we see that MDR-TB prevalence in China is very high when compared to the global estimated average of 4.8%.

China’s high MDR-TB prevalence can be attributed to a combination of high transmission rates and different health services related risk factors, patient behavior related risk factors, socio-demographic related risk factors and epidemiological risk factors. MDR-TB either develops in a patient or is transmitted from a MDR-TB patient to another individual. One of the most significant findings of the study conducted on patients in the Shandong TB hospital was that among the included MDR-TB patients, recent transmission seemed to be responsible for most cases, as determined by genotype clustering data. In addition, MDR-TB was associated with previous TB treatment, lower socio-economic status, and the Beijing genotype TB strain (Chapter 3). The relationship between MDR-TB and the Beijing genotype TB strain is complex. One potential reason for this is that the Beijing genotype TB strain may develop into MDR-TB more easily than other strains, however, proving this would require further in-depth biological studies of its mutation patterns.

Aside from prevention of transmission, addressing the high rates of MDR-TB in China requires an aggressive and appropriate TB control program with effective treatment regimens which incorporate programmatic management of drug-resistant TB. However, the misuse of second-line drugs and/or mismanagement of TB treatment can compound the problem of MDR-TB further by creating conditions in which drug resistance is more likely to develop. Two examples of mistreatment frequently observed in China are the treatment of MDR-TB cases with first line drugs and the treatment of non MDR-TB cases with second line drugs without the aid of a drug susceptibility test (as testing is only available at very few sites).

Regarding the issue of treatment of MDR-TB with first-line drugs, our investigation found that MDR-TB patients had high recurrence and death rates four years after treatment with standardized first line drug regimens, contradicting the reported high cure rate of MDR-TB with standardized first line drug regimens in Heilongjiang province. Also, the cure rate with standardized first line drug regimens for MDR-TB patients in Heilongjiang province was higher than what was observed in other countries. This provided evidence that conventional smear microscopy used to determine the treatment
outcome for MDR-TB cases or the reporting and recording method and quality or both were flawed (Chapter 4).

Regarding second-line drug treatment, our findings suggested that the drug regimens available for effective MDR-TB treatment were potentially inadequate and when second line drugs were used to treat already resistant strains of MDR-TB without drug resistant testing, the potential for XDR-TB development was created. Furthermore, second line drugs are widely available in China for the treatment of TB and other diseases. But, only a fraction of the facilities which diagnose and treat (drug resistant) TB patients possess the resources to perform drug susceptibility testing or despite possessing the resources do not routinely use the 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 about half of the facilities (Chapter 5). 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 the most important predictors of second line drug availability and use. Larger facilities at the provincial and prefecture levels (where more patients seek health care) were more likely to possess second line drugs. Furthermore, in the facilities where second line drugs were available for the treatment of MDR-TB, fewer than three classes of second line drugs were available in nearly a third of the facilities when at least 3 classes of second line drugs should be available.

The two studies mentioned above indicated widespread misuse of first and second-line TB drugs and merited an additional study to further investigate the extent of inappropriate TB treatment regimens in China (Chapter 6). In six TB hospitals in China, only 18% of patients with new cases and 9% of patients with retreatment cases were given standard TB treatment regimens as prescribed by the Chinese National Tuberculosis Control Program. The widespread prevalence of incorrect TB treatment regimens in China heightens the risk for the development of drug-resistant TB. Despite the fact that these TB hospitals had better equipment and more well-trained medical staff than the TB centers, there was still a pervasive lack of adherence to accepted and established TB treatment protocols (Chapter 6).
In addition to treatment mismanagement, the proliferation of drug resistant tuberculosis in China can also be partly attributed to enhanced transmission due to poor infection control and prevention practices. An assessment of these practices in TB centers in Henan, China showed that only a minority of the centers separated patient consultation areas and X-ray areas from the waiting areas and administrative areas. Proper and controlled 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. Not surprisingly, the latent TB infection prevalence of health care workers with Bacille Calmette-Guerin scar was 55.6%. Older health care workers, health care workers with longer durations of employment, and health care workers who worked in departments with increased contact with TB patients had a higher prevalence of latent TB infection. Health care workers who work in TB centers at the prefecture level, or with an inpatient ward also had a higher prevalence of latent TB infection. In all these cases, the data overwhelmingly reflects a situation in which higher TB transmission occurred due to increased exposure and poor infection control practices. Overall, the TB prevalence was 6.7/1000 among medical staff much higher than that of the general population (Chapter 7). TB infection control in TB centers in Henan, China, is currently inadequate and the prevalence of latent TB infection and TB disease among health care workers was high.

In conclusion, MDR-TB prevalence remains a huge challenge for TB control in China. The results of our studies indicated that high MDR-TB prevalence in China was caused by high transmission rates due to inadequate infection control, and the lack of appropriate drug susceptibility testing result-based drug regimens. Furthermore, there was ample evidence that the methods used to determine treatment outcomes as well as the reporting systems were flawed and must be improved to more accurately assess the TB situation in China. Finally, the presence of the Beijing genotype TB strain, retreatment cases, and lower socio-economic status were all associated with MDR-TB, suggesting future TB control policies should be designed to account for these specific associations.

**STUDY LIMITATIONS AND CHALLENGES**

The studies presented in this thesis cover a wide range of topics including MDR-TB prevalence, transmission, and risk factors, and each study possessed unique challenges
regarding the amount of information available for conducting research as well as the quality of the information itself. Here, the limitations related to the different studies are described, including sampling bias, selection bias within the sample, and information bias.

Sampling bias encountered in several of the studies involved restricted geographical locations or specific organizations which may have not been representative to accurately gauge relevant MDR-TB related trends throughout all of China. For example, in the study involving the prevalence of TB drug resistance in China, data was available for only 10 provinces and any trends garnered from this information reflect national trends only insomuch as these 10 provinces are representative of all of China. The drug regimen study (Chapter 6) presented a similar problem because only six TB hospitals were investigated and the reported results may not be representative of all TB hospitals in China. Aside from this, the sampling method for the drug resistance surveys in the 10 provinces (Chapter 2) was based only on new cases in accordance with the guidelines for surveillance of drug resistance in TB. Moreover, this study only selected participants from TB centers. Although TB centers treat first-time retreatment cases free of charge, the diagnosis and treatment is not free of charge for patients treated more than two times, including chronic TB cases. These TB cases, who are the most likely candidates for MDR-TB, may be more likely to go to TB hospitals as they generally have better health care equipment and more experienced staff than TB centers. Therefore, conducting studies solely based on patients at TB centers may artificially select for retreatment cases that are less likely to have MDR-TB, resulting in an underestimation of MDR-TB prevalence in previously treated TB cases. Because the number of new cases in this survey greatly outnumbered the number of retreatment cases, the sample size for retreatment cases was most likely insufficient to accurately gauge drug resistance in retreatment cases. The study on MDR-TB genotyping (Chapter 3), presented an interesting challenge on how to obtain a representative sample that covers all cases in certain areas. In this study, although a sufficient number of patients were recruited to determine genotype clustering, these patients all originated from the same large TB hospital. There was no genotype data from other hospitals available and any transmission of TB from a patient at the hospital studied to an individual who sought health care at another hospital would go unaccounted for. Thus our results likely underestimate the clustering proportion.
Selection bias posed another concern. Several studies did not incorporate a random selection method. For example, for the second line drug usage study (Chapter 5), clinics were not randomly selected, and large hospitals were overrepresented. Larger hospitals are expected to have greater access to second line drugs, which would overestimate second line drug availability in our study compared to the national average. However, as second line drugs are widely available at all levels, this most likely does not greatly influence our results especially because larger hospitals generally treat more patients and thus expose more patients to second line drugs. The study involving the follow-up survey of MDR-TB treatment outcomes in Heilongjiang (Chapter 4) provides another instance of possible selection bias due to loss to follow up. In this case, the cohort size was sufficiently large, however, only slightly more than half of the patients in the cohort could be included four years later in the follow up survey. This situation was not entirely unexpected considering the tendency of many Chinese individuals to frequently relocate to another area in which case establishing contact would prove very difficult. The status of these individuals and their state of health were unknown. To circumvent this limitation, a highly conservative sensitivity analysis in which we assumed that all the non-included patients were alive and did not have recurrent TB, still showed high recurrence and death rates.

Information bias should also be considered. In Chapter 5, estimates of second line drug availability provided by TB centers may be inaccurate, tending towards underestimation, as second line drug use is not recommended by the National TB Control Program. Although the information used in this study as well as all other studies is assumed to be accurate, inaccurate reporting of data always poses a risk and the extent to which it may influence the studies’ results is taken into consideration. In the drug resistance surveys in 10 provinces of China (Chapter 2), patients may not have been willing to disclose their treatment history because the policy did not include completely free TB re-treatment for Henan (1996) and Zhejiang during the study period. The patients may have actually been retreatment cases, but the reporting does not necessarily reflect this. In the cases in which project staff were directly responsible for reporting data regarding their own health care facilities, such as in the infection control study (Chapter 7), the reporting of prevailing poor TB infection control practices may be inaccurate, tending towards underestimation of infection control related problems. Besides false reporting, inaccurate reporting may also be due to unreliable assays. For the follow-up survey of MDR-TB treatment outcomes in Heilongjiang (Chapter 4), the 2005 reported cure rate
for MDR-TB patients was 83% among new and 66% among retreatment patients treated with a standardized first line drug treatment. These reported figures were assumed to be inaccurate because of their inconsistence with reported figures for other countries and can most likely be attributable to the use of sputum smear microscopy testing as a determinant for treatment outcome. A lack of relevant data also posed a problem for the second line drug usage study (Chapter 5). Precise information on the exact quantities of second line drugs used was not collected, but only whether second line drugs were available at all. We requested data on actual use (amount of drugs used in the previous year and actual treatment regimens) but did not receive this, probably because the data was not available or because of reluctance to provide information on regimens that do not follow national policy. We also could not obtain information on the reasons for incorporating second line drugs into the treatment regimen.

Despite these limitations, we were able to draw important conclusions on the epidemiology and control of multidrug resistant tuberculosis as described above.

**CHALLENGES AND PROPOSED SOLUTIONS FOR MDR-TB CONTROL AND PREVENTION IN CHINA**

The first nationwide drug-resistant survey was conducted in 2007-2008. The sampling for this survey considered both new cases and previously treated cases and reported an overall MDR-TB prevalence of 8.3% (5.7% in new cases and 25.6% in previously treated cases). In comparing the results of the ten provinces’ drug-resistant survey for the average MDR-TB prevalence (5.4%) among new cases (conducted from 1996 to 2004) to the national drug resistant survey (Chapter 2), we found that the MDR-TB prevalence rates were nearly the same and remained high, posing a huge burden for TB prevention and control in China. Furthermore, the MDR-TB prevalence as measured by the nationwide TB prevalence survey showed no significant difference between 2000 (7.6% (95% CI 4.7%-11.5%)) and 2010 (5.4% (95% CI 2.9%-9.0%)). Due to lack of statistical power, it was not possible to establish whether a significant change actually occurred between the different surveys. Also, the sampling methods were not completely similar, further complicating a comparison. Nevertheless, the number of MDR-TB cases in China remains high and the reasons for this should be clearly understood to improve the situation.
China’s economy has developed very rapidly in recent years, and China has achieved the global targets for TB control in 2005, including 100% DOTS coverage, an estimated case detection rate above 70%, and a reported cure rate higher than 85%, 34,35 and has maintained these targets until now. 36 However, there are still several fundamental problems - in addition to China’s huge number of MDR-TB cases and inconsistent DOTS implementation - which make long-term MDR-TB control in China extremely difficult. 2,6,37-40 These challenges primarily include insufficient resources, inadequate diagnosis methods, improper treatment, poor patient compliance, poor infection control practices, 41 a lack of dedicated MDR-TB control legislation, and slow expansion of programmatic management of drug-resistant TB. Strong interventions should be taken for MDR-TB control promptly to halt the rapid spread of MDR-TB in China. 42,43 The following paragraphs describe in detail the most significant problems identified regarding MDR-TB control and prevention in China and provide feasible solutions for addressing these problems.

1) Lack of funding and resources. Due to a lack of funding and human resources, 44,45 the programmatic management of drug-resistant TB in China is expanding very slowly and currently only covers a small proportion of the population. 44 Facing this challenge, sustained political commitment is essential to establishing and maintaining a nationwide MDR-TB control program in China. The main components include adequate infrastructure, development and retention of human resources, proper equipment and sufficient program funding, especially for extended drug susceptibility testing and programmatic management of drug-resistant TB (Chapters 4, 5, 6). Enhanced advocacy, communication and social mobilization should be used to inform all stakeholders about the serious situation on the epidemic of MDR-TB and the importance of reducing the disease burden in China (Chapter 2). Consequently, obtaining sufficient and continuous investment of resources is required to improve access to MDR-TB detection and treatment in China. 46

2) Inadequate diagnostic methods and limited management. Accurate, timely diagnosis is another key element of MDR-TB control. MDR-TB must be diagnosed correctly before it can be treated effectively. 46 Case-finding strategies should vary depending on the epidemiological situation and local capacity (Chapter 3). Conventional MDR-TB drug susceptibility testing (DST) methods can take up to 2-3 months, however, and because MDR-TB treatment conversion itself is also very slow, both of these factors
combine to further prolong the transmission period. Therefore, these methods may not be suitable for areas of China in which TB transmission poses a heightened threat. Instead, more rapid drug susceptibility testing methods such as the Hain “GenoType® MTBDR plus” and the Xpert MTB/RIF test should be used. Currently, free drug susceptibility testing in China is available only for MDR-TB suspects at prefecture MDR-TB diagnosis and treatment centers that are covered by the Global Fund project, using conventional slow methods. MDR-TB suspects are defined as smear positive TB patients in close contact with MDR-TB patients, smear positive retreatment cases including chronic cases, and new TB patients with positive sputum smear microscopy results at the end of 3 months of treatment. However, to date there are still very few MDR-TB diagnosis and treatment centers that are covered by the Global Fund Project in China. Therefore, to improve MDR-TB diagnosis, rapid sputum culture and drug susceptibility testing tools such as Xpert MTB/RIF should be implemented at the county level and higher to improve case detection. Rifampin-resistant patients detected by Xpert MTB/RIF can then be referred to the MDR-TB diagnosis and treatment center in a timely manner, thereby reducing disease transmission. Moreover, the programmatic management of drug-resistant TB in China should be rapidly expanded to cover the entire country to ensure that all MDR-TB cases are able to access standardized MDR-TB care (Chapter 4).

3) Improper treatment and compliance. MDR-TB prevention and control in China also faces problems with improper treatment and drug regimens (Chapters 4, 5, 6). Our findings suggested that the drug regimens available for effective MDR-TB treatment were potentially inadequate and when second line drugs were used to treat already resistant strains of MDR-TB without drug-resistant testing, the potential for XDR-TB development was significantly increased. Furthermore, second line drugs are widely available in China for the treatment of both TB and other diseases. But, only a fraction of the facilities which diagnose and treat (drug resistant) TB patients possess the resources to perform drug susceptibility testing or despite possessing the resources do not routinely use the testing to guide their choice of treatment regimen. To improve treatment outcomes, all sputum smear positive TB patients should have (preferably rapid) drug susceptibility testing performed for first line drugs. Then, if the TB patients are identified as MDR-TB patients, MDR-TB treatment regimens should be based on these drug susceptibility testing results. In China, XDR-TB also poses a risk due to inappropriate treatment (Chapters 5, 6), and the development of drug susceptibility
testing capacity by laboratories for second-line injectable drugs and fluoroquinolones in order to more effectively diagnose XDR-TB and prescribe more appropriate XDR-TB drug regimens is paramount. To improve M/XDR-TB treatment, a successful treatment strategy consisting of a rational method for designing the optimal treatment regimen, a patient-centered approach for delivering this regimen with DOT, and a plan for monitoring and managing adverse drug reactions should be implemented.

Improving patient compliance is also very important. Several retrospective studies have already shown that treatment compliance was very low in some areas of China. As MDR-TB diagnosis and treatment centers are only available at the prefecture level, patients in remote areas or larger prefectures (populations greater than 10 million) may be unwilling or unable to travel long distances for medical care. Requiring these patients to travel long distances risks compounding the problem of transmission even further, especially when public transportation is used by those patients willing to seek treatment. More MDR-TB diagnosis and treatment centers should be established in large cities and prefectures as well as remote areas to facilitate greater access of diagnosis and treatment among all patients. Furthermore, subsidies for transportation, food and other related costs for poor patients should also be provided to improve patient compliance and increase the number of patients seeking care.

4) Poor infection control practices. The proliferation of MDR-TB in China is also partly attributed to enhanced transmission due to poor infection control and prevention practices (Chapter 7). Recommendations for MDR-TB infection control are essentially the same as those for drug-susceptible TB with only minor differences in emphasis. Further information is provided in the WHO policy on TB infection control in health-care facilities, congregate settings and households. China should improve administrative controls, environmental/engineering controls, and personal respiratory protection in health care facilities.

5) Inaccurate reporting and recording methods. Our investigation showed MDR-TB patients in Heilongjiang province in China had high cure rates with standardized first line drug regimens (83% among new and 66% among retreatment patients), but also had high recurrence and death rates four years after treatment with standardized first line drug regimens, indicating the method used to determine the treatment outcome or the reporting/recording method and quality or both were flawed (Chapter 4). An
improved TB reporting and recording system should also be implemented to ensure reliable, accurate, complete, and timely surveillance data (Chapter 4). The continuous supervision and monitoring/evaluation of TB reporting and recording system at all levels should be strengthened according to a set of specific objectives, and sufficient training and assigned responsibilities for all relevant staff members should be provided to improve system quality. Regular in-depth analysis of surveillance data and assessments of data quality can help identify weakness in the TB reporting and recording system. TB data should be regularly cross checked among a number of sources, including TB register, medical records, TB laboratory register, blind re-testing of sputum smear slides, and directly obtaining information from the patients.

6) Poor quality control and assurance. Quality-assured culture and drug susceptibility testing are indispensable. Non-viable cultures, culture contamination, and unreliable drug susceptibility testing results have major consequences for both individual patients and the National TB Control Program as a whole (Chapter 5,6). Internal quality control and external quality assurance, including a link for proficiency testing with a recognized reference laboratory such as one of the WHO-recognized super reference laboratories, should be a major consideration (Chapter 2), and only drugs that have been quality-assured by a stringent drug regulatory authority recognized by the WHO, a WHO prequalification program or one that meets the WHO Good Manufacturing Practice standards should be used.

7) Lack of targeted legislation. Currently there are no official policies in place which are specifically designed to improve MDR-TB control and prevention in China. Government policy should be made to ensure appropriate usage of second line drugs and prevent further development of drug resistance. Legislation which clearly defines the responsibilities and duties of M/XDR-TB patients’ to prevent transmission (e.g. travel restrictions and providing masks for hospital and other public visits) should also be implemented. Finally, specific regulations should be outlined which protect the groups who have the highest exposure to (i.e. have the highest risk of being infected with or developing) MDR-TB, for example, health care workers. Regular screening for TB, N95 respirators and infection control education should to be available to protect health care workers.
FURTHER RESEARCH

Considering the high prevalence of MDR-TB in China, expansion of drug susceptibility testing alongside more-standardized treatment regimens should be a top priority. However, drug susceptibility testing coverage varies greatly in different regions in China, and capacity building may take a long time. Prior to the overall coverage of drug susceptibility testing in China, provincial drug-resistant surveys should be conducted periodically to obtain base-line data as well as to assess the trends of MDR-TB burden and control over time in different provinces. TB drug resistance trends should also be monitored routinely on a national scale. This would provide scientific evidence to guide MDR-TB control and prevention policy and interventions.

To investigate the risk factors associated with poor DOTS quality, a well designed DOTS quality evaluation using both qualitative and quantitative methods should be conducted on a national scale. This DOTS evaluation should include an investigation of which the different TB treatment regimens, dosages, and administration frequencies and schedules of the different TB drugs used in health facilities nationwide. In addition, the currently used reporting and/or recording methods should be thoroughly evaluated to further improve the quality of the system. Based on the assessment findings, action to improve areas where quality of implementation is lacking should be taken to prevent further development of M/XDR-TB.

The assessment and development of tools for the rapid testing of drug resistance are necessary to efficiently stop the ongoing transmission of M/XDR-TB through early diagnosis and effective treatment. There are several new diagnostic tools which have recently become available including Xpert MTB/RIF and the Hain “GenoType® MTBDR plus” test. Well designed operational research on diagnostic tools evaluation including each tool’s sensitivity, specificity, accuracy, rapidness, and affordability will provide valuable data on selecting the most suitable tools for rapid case detection of MDR-TB in China.

The current MDR-TB regimen generally last over two years and may lead to poor patient compliance, and consequently, low cure rates. Because all new drugs need to be evaluated and approved by associated authorities prior to entering the Chinese market, it may take some time to incorporate them into TB treatment regimens. To foster a
rapid registration and usage of new drugs, randomized clinical trials are now urgently needed to develop new regimens including new drugs, for example TMC207,\textsuperscript{58} for improved treatment outcomes of patients with M/XDR-TB in China. The development of new potent drugs with a low toxicity profile, allowing for shorter and more effective treatment against TB, further exploration of the role of possible adjunctive therapies, such as vitamin D supplementation,\textsuperscript{59} and the use of existing compounds with novel anti-mycobacterial mechanisms, such as thioridazine, should also be a priority.\textsuperscript{60,61}

Assessment of the current Global Fund MDR-TB control model is needed to establish a suitable MDR-TB control model in China. On-site investigation by multidisciplinary expert teams should examine the suitability of the program in the following areas: funding, resources, the location of MDR-TB diagnosis and treatment centers, the responsibilities of different levels of health care facilities, diagnosis and case detection, treatment and management of patients, laboratory responsibility and capacity building at the different levels, and drug management.\textsuperscript{61} Based on the findings of the assessment, the current Global Fund MDR-TB control model should be improved and adjusted.

Finally, cohort studies on the molecular epidemiology of M/XDR-TB and their associated risk factors with representative samples in several restricted areas in China should also be conducted. These studies should focus on developing a better understanding of the way in which epidemiological risk factors (e.g. molecular genotype) and socioeconomic and demographic risk factors (e.g. occupation, smoking habits) affect transmission, the current control status of MDR-TB transmission, and the effect of using inappropriate treatment regimens on producing MDR-TB in patients. The results of these studies could significantly aid in the development of TB prevention and control policies in different regions throughout China.

**OVERALL CONCLUSION**

In conclusion, this thesis showed that MDR-TB prevalence is still a huge challenge for TB control in China. Our findings indicated that contributing factors to MDR-TB in China included inappropriate TB treatment regimens, the lack of drug susceptibility testing result-based drug regimens, and inadequate infection control. Presence of the Beijing genotype TB strain, retreatment cases and lower socio-economic status were important risk factors for MDR-TB. MDR-TB patients deemed to have been cured
had high recurrence and death rates four years after treatment with standardized first line drug regimens, indicating a lingering problem with the accuracy of currently used reporting and recording systems and a sustained need to improve the quality of DOTS implementation in China. Prevention of drug resistance through adherence to proper standards of care and control is imperative and should be a top priority for all TB control efforts. 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 limited 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, and strong intervention for MDR-TB control should occur promptly to halt and eventually reverse the spread of MDR-TB in China.
REFERENCES


