Epidemiology and control of multidrug-resistant tuberculosis in China

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CHAPTER 1

GENERAL INTRODUCTION
INTRODUCTION

With over 9 million cases and nearly 2 million deaths annually, tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. Anti-TB drugs were first developed over 60 years ago and have since been used for the effective treatment of TB patients, and over this extended period, different TB strains have had ample time to develop drug resistance. Some strains of *Mycobacterium tuberculosis* (*M. tuberculosis*) already resistant to a widely used drug, isoniazid, eventually also became resistant to rifampicin after the drug’s discovery in 1966 and widespread use since 1970. Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampicin, has emerged as an important global public health problem. As these patients carry strains resistant to the two most effective first line drugs, curing MDR-TB patients is very difficult. In the last decade, the resistance patterns of different MDR-TB strains have broadened to extensively drug-resistant TB (XDR-TB). XDR-TB is defined as MDR-TB plus resistance to any fluoroquinolone and at least one of three available injectable second line drugs (i.e. amikacin, kanamycin, capreomycin).

Drug resistance is a serious threat to TB control, and the recognition of XDR-TB, has further highlighted this threat.

DEVELOPMENT MECHANISM FOR DRUG-RESISTANT TUBERCULOSIS

Drug-resistant TB originates from random mutation, with a frequency of mutation ranging from $10^{-10} - 10^{-7}$, in a population of *M. tuberculosis* bacteria. During anti-TB treatment, clinically significant drug resistance in TB can develop. Anti-TB drugs impose a selection pressure in *M. tuberculosis* populations that results in decline of the drug susceptible population and growth of resistant mutants that thus gradually emerge as the dominant strain. The emergence of drug resistance during monotherapy of TB has been observed since the 1940’s when streptomycin was used in isolation for treatment of the disease. To solve this problem, paraaminosalicylic acid and subsequently isoniazid were incorporated into the drug regimen. Resistant TB strains which emerged during TB treatment may subsequently be transmitted to others in the patient’s community. Therefore, people can be infected with and develop active drug-resistant TB without having been treated previously.
The first national survey of TB drug resistance among patients who were not previously treated took place in Britain from 1955–1956 revealing the existence of primary resistance to streptomycin, paraaminosalicylic acid and isoniazid. This discovery led to the establishment of triple drug therapy, as treatment of patients with a two-drug regimen when the patient possessed a strain of TB already resistant to a single first-line drug, was likely equivalent to monotherapy, especially problematic in the presence of a sizeable bacillary load.17

Second-line drugs were used to complement first-line drugs to treat drug-resistant TB. Among these drugs, a class known as fluoroquinolones proved to be one of the most effective types of drugs for treatment. Unfortunately, fluoroquinolones are frequently used to treat respiratory tract infections in patients who may in fact have TB.18-20 Because of the effectiveness of the fluoroquinolones in treating respiratory tract infections and their likely ability to mask TB symptoms in the short-term, this therapeutic practice may delay the diagnosis of TB, and facilitate the development of fluoroquinolone resistant TB, particularly in TB high burden countries.21,22 Since culture and drug susceptibility testing are not routinely available in many settings, even combination therapy may have the same effect as a monotherapy, which may play an important role in the development of drug resistance.23,24

Poor compliance to TB treatment is a key factor in the development of drug resistance. Even if a proper drug regimen incorporating a combination-type therapy is prescribed, if taken irregularly, patients infected with susceptible M. tuberculosis strains can still develop drug-resistance.6 Mitchison has proposed four basic mechanisms by which drug resistance may emerge as a result of poor treatment compliance: differential bactericidal effects during initial killing, monotherapy during sterilization of special populations, differential sub-inhibitory drug concentrations during regrowth, and differential bacterio-pausal effects during regrowth.25 Differential bactericidal effects during initial killing refers to differences in the amount of bacteria initially killed by different drugs in the first few days of treatment. For example, the drug isoniazid in an isoniazid/rifampicin treatment regimen kills M. tuberculosis bacteria more rapidly than rifampicin at the start of treatment. This means that in the first few days of treatment, isoniazid resistant strains are selected while the full effects of rifampicin have still not taken effect. Monotherapy during sterilization of special populations occurs because only certain drugs such as rifampicin and pyrazinamide have proven to be effective
against special sub-populations of bacteria which show spurs of growth or thrive in acidic environments. Differential sub-inhibitory drug concentrations during regrowth refers to the selection of drug resistant mutants during a period of bacterial regrowth in which low drug concentrations in the patient slow down bacterial growth for drug sensitive strains but exhibit no effect on resistant strains. Since different drugs have different pharmacokinetics and different margins of effectiveness, interrupting drug intake may lead to temporary monotherapy. This may apply in particular to isoniazid which has both a long half-life and a high therapeutic margin. Finally, differential bacterio-pausal effects refers to the difference in lag periods for different anti-TB drugs. For example, after initial exposure to isoniazid, isoniazid-sensitive bacteria remain inhibited for a period of up to 7 days. However, this lag period is much shorter (~2-3 days) for rifampicin, and if initial exposure to both rifampicin and isoniazid is followed by a period in which no medication is taken, isoniazid resistant strains may be selected over isoniazid susceptible strains, since within a few days after stopping therapy they are also not inhibited by rifampicin any more. This mechanism would favour in particular resistance to streptomycin and isoniazid since they have the longest lag periods.\(^{24}\)

Among the first-line drugs, isoniazid has the strongest early bactericidal activity, regardless of bacillary load, and is most capable of preventing the emergence of strain resistance to companion drugs.\(^{25}\) However, if isoniazid monotherapy is used for treatment of presumed latent TB infection, and patients actually have active TB and are not diagnosed in a timely manner, the chances of developing isoniazid resistance drastically increase.\(^{23,26}\) The long history of prescribing isoniazid and streptomycin for the treatment of TB as well as genetic mutations caused by the drugs themselves might be the main reasons for the observed high frequency of isoniazid and/or streptomycin resistance among new patients in most settings.\(^{27}\) In HIV-infected patients, rifampicin monoresistance may emerge prior to isoniazid resistance due to the inhibitory effects between rifampicin and certain antiretroviral drugs that lower its effective concentration in the body.\(^{28,29}\)

In addition to monotherapy and poor compliance, inadequate dosage and poor quality of drugs are also important factors in the development of drug resistance. Currently, no single genetic mutation has been identified as the source of resistance of two or more anti-TB drugs.\(^{30}\) The currently accepted model for development of resistance in TB is therefore that resistance commences first with mono-resistance, and subsequent
resistance to additional drugs may occur. Resistance to multiple TB drugs is thus the cumulative result of sequential mutations.\textsuperscript{30} It is difficult to determine how drug resistance has developed among retreatment cases as this group contains a combination of patients with three types of resistance: (1) patients who have acquired resistance during TB treatment, (2) patients who have been primarily infected with a resistant strain and subsequently failed therapy, and (3) patients who have been re-infected with a resistant strain.\textsuperscript{7} In order to differentiate such patients, a cohort study among TB patients may be conducted using drug susceptibility testing and DNA fingerprinting of the isolates at the onset of treatment and at the onset of a subsequent recurrent episode.\textsuperscript{31}

**RISK FACTORS FOR DRUG-RESISTANT TB**

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, detailed in Table 1.\textsuperscript{32-36} A number of factors listed in Table 1 have been identified as the main reasons for the emergence of drug-resistant TB epidemics in some countries.\textsuperscript{33} 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.\textsuperscript{37} Before 1993, very few countries had implemented national strategies similar to DOTS.\textsuperscript{38-40} Until MDR-TB was recognized as an epidemic ten years ago, the DOTS strategy covered less than half of the global population.\textsuperscript{40} Without proper TB control and prevention strategy implementation, the number of MDR-TB cases will undoubtedly rise. As mentioned earlier, the shortage of supply or poor quality of drugs, and inappropriate adherence to drug regimens by patients are important risk factors for development of drug-resistant TB. Other risk factors for drug-resistant TB and MDR-TB such as inadequate infection control in health care facilities, the prevalence of highly virulent MDR-TB strains of *M. tuberculosis* such as the Beijing genotype,\textsuperscript{32-34, 41,42} previous TB treatment,\textsuperscript{43,44} female sex (due to a lower social status within the family),\textsuperscript{44} young age,\textsuperscript{45,46} urban residency,\textsuperscript{46} migrants,\textsuperscript{45,46} patients with high frequency of travel,\textsuperscript{46} low socio-economic status,\textsuperscript{43} alcoholism, smoking,\textsuperscript{43} and lung cavities leading to high bacillary load have also recently been reported.\textsuperscript{43} Several risk factors for XDR-TB including an increased number of previously received second line drugs, increased previous treatment duration and female sex have also been identified.\textsuperscript{47}
Several of the factors mentioned in Table 1, including the lack of full supervision during the intensive phase of treatment, the major influence of the private sector in some countries with a high MDR-TB burden, and the inadequate infection control measures in many middle- and low-income countries are very difficult to address. Moreover, the transmission mechanisms of MDR-TB strains in most parts of the world are not fully understood.

Table 1. Risk factors for drug-resistant tuberculosis.

<table>
<thead>
<tr>
<th>Health service related risk factors</th>
<th>Patient behavior-related risk factors</th>
<th>Demographic-related risk factors</th>
<th>Epidemiological risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly organised or funded NTPs</td>
<td>Inadequate drug intake</td>
<td>Female sex / family social status</td>
<td>High prevalence of highly virulent MDR strains of M. tuberculosis</td>
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<td>Guidelines inadequate or lacking</td>
<td>Poor compliance or non-adherence to treatment</td>
<td>Young age</td>
<td>HIV infection in some regions</td>
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<td>Non-implementation of DOTS</td>
<td>Lack of money (treatment not available free of charge)</td>
<td>Low education</td>
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<tr>
<td>Insufficient quality of DOTS</td>
<td>Substance dependency disorders</td>
<td>Low income</td>
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<tr>
<td>Lack of treatment monitoring</td>
<td>Social barriers</td>
<td>Occupation including transport workers and farmers</td>
<td></td>
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<tr>
<td>Non-standardized treatment</td>
<td>Malabsorption of TB drugs</td>
<td>Migration history</td>
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<tr>
<td>Inadequate supply or poor quality of drugs</td>
<td>Frequency of travel</td>
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<td>History of frequent shortages of drug supplies in the country</td>
<td>Alcohol consumption</td>
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<tr>
<td>Wrong dose or combination</td>
<td>Smoking</td>
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<tr>
<td>Poor infection control in health centers and hospitals</td>
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<tr>
<td>Dominant private sector</td>
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<td>Poor training of health care workers</td>
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</tbody>
</table>

MDR-TB=multidrug-resistant tuberculosis; NTP=National Tuberculosis Programme; HIV=human immunodeficiency virus.
THE CURRENT STATE OF GLOBAL DRUG-RESISTANT TUBERCULOSIS

In 2007, the World Health Organization (WHO) released the fourth report on global anti-TB drug resistance,7,55 which includes data for drug susceptibility testing of 90,726 patients from 83 countries and provides the latest data on the extent of drug-resistant TB between 2002 and 2007.55 The report states that the median prevalence of MDR-TB among new TB cases was 1.6%, ranging from 0% in eight low prevalence countries to 22.3% in Baku, Azerbaijan.55 The two areas with the highest MDR-TB prevalence in new cases were China, with higher than 6% in with two different settings, and the former Soviet Union, with higher than 6% in twelve different settings.7 This report also found that the median prevalence of MDR-TB in retreatment cases was 11.7%.55 Six countries reported no MDR-TB patients, whereas 55.8% of retreatment cases in Baku (Azerbaijan) and 60% in Tashkent (Uzbekistan) were MDR-TB cases. The report found 17 different settings with a high (over 25%) prevalence of MDR-TB in retreatment cases. Among these, nine settings were located in former Soviet Union countries.7 At least one country in all six WHO regions reported 3% or higher MDR-TB prevalence among newly diagnosed TB cases.7 In Europe (including the former Soviet Union), the average prevalence of patients with MDR-TB among both new and retreatment cases was 4.0%.7,55 In the South-East Asia Region, Myanmar reported the highest prevalence of MDR-TB among new cases (4%), and Thailand reported the highest prevalence among previously treated cases (34.5%).7

In countries without MDR-TB surveillance, the number of new and retreatment cases is often estimated, and drug resistance data can be used to estimate the proportion and total number of MDR-TB cases.7 According to the WHO, in 2006, the estimated number of global incident MDR-TB cases was 489,139 accounting for 4.8% of the total estimated number of global incident TB cases.7,55 This was higher than the 458,000 estimated number of incident MDR-TB cases accounting for 4.4% in 2003.56,57 In both 2003 and 2006, China and India accounted for approximately half of the global estimated number of incident MDR-TB cases.7,55,57
DRUG RESISTANT TB AND ITS CONTROL IN CHINA

China is situated in the eastern part of Asia, on the west coast of the Pacific Ocean, and has a total land area of 9.6 million square kilometers. The distance from east to west measures over 5,200 kilometers, and from north to south, over 5,500 kilometers. China has a land border of 22,143.34 kilometers and is bordered by fourteen countries: North Korea in the east; Russian in the northeast and the northwest; Mongolia in the north; India, Pakistan, Afghanistan, Tajikistan, Kyrgyzstan, Kazakhstan, Bhutan and Nepal in part of the west and the southwest; Burma, Laos and Vietnam in the south. According to the China Statistics Yearbook (2009), there are 31 provinces, autonomous regions, and municipalities in mainland China directly under the Central Government including 333 prefectures/cities, 2859 counties/districts, and a population of 1.3 billion in 2008.

TB is a major public health problem in China. According to the 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. Since China joined the global project on anti-TB drug resistance surveillance organized by the WHO and the International Union Against Tuberculosis and Lung Disease in 1996, 10 provinces have reported MDR-TB prevalence data. The MDR-TB prevalence rates reported by the different provinces vary greatly, ranging from 3.5% to 23.3% among all TB cases (2.1% to 10.8% among new cases, 11.7% to 41.9% among previously treated cases). The first national drug resistance survey in 2007-2008 randomly selected 70 counties all over China. An overall MDR-TB prevalence of 8.3% (5.7% in new cases and 25.6% in previously treated cases) was reported with 0.7% (0.5% in new cases and 2.1% in previously treated cases) of cases classified as XDR-TB. Some TB hospitals in China have also reported TB strains resistant to all types of second line drugs. The national anti-TB drug resistance baseline surveillance report in 2007 estimated that 120,000 new MDR-TB cases (including 9000 XDR-TB cases) emerged annually in China, accounting for approximately 24% of the global burden of MDR-TB. The distribution of MDR-TB cases showed that most of the cases were adults from rural areas. Poor compliance and inappropriate treatment were identified as the key risk factors for MDR-TB occurrence.
Despite the serious nature of TB, the country’s progress in TB control was slow during the 1990s and up until 2003. The estimated proportion of new cases of sputum smear positive TB that were diagnosed and treated by the public health program—a key indicator of TB control efforts—had stagnated at around 30%, far below the 70% target set by the WHO. Since 2003, the Chinese government has been implementing a series of measures to strengthen the public health system. Within 3 years, the implementation of the WHO recommended DOTS strategy for TB control increased from 68% to 100% in all counties and the detection of new smear-positive TB cases by the public health system more than doubled from 30% to 80%. Together with a reported TB treatment success rate of more than 90%, China achieved the 2005 global targets for TB control.

In the context of the new Stop TB Strategy, launched in 2006 by the WHO in conjunction with the Stop TB Partnership, 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 had covered 41 prefectures/cities in 12 provinces in which 14609 MDR-TB suspects were screened, and 1978 (13.5%) MDR-TB cases were identified. Among these MDR-TB cases, 1049 (53.0%) cases were treated with a standardized treatment regimen recommended by the WHO. By that time, and the culture negative rate was 65.2%. 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.

STRUCTURE OF THIS THESIS

This thesis focuses on programmatic issues related to MDR-TB control and prevention in China, incorporating research findings on MDR-TB epidemiology, transmission, risk factors, treatment regimens and second line drug usage status.

Chapter 1 provides a general overview of MDR-TB epidemiology, development, transmission and its risk factors globally, and MDR-TB control in China.

Chapter 2 presents an overview of the results of the drug-resistance surveys conducted in ten provinces in China between 1996 and 2004 which indicate MDR-TB levels
INRODUCTION

varied greatly between provinces in China. Estimates of the drug-resistance rates were adjusted to take into account the results of retesting a random sample (11.6%) of all isolates from those provincial surveys.

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.

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 conventional smear microscopy as a predictor of long-term outcomes is evaluated.

Chapter 5 and Chapter 6 assess the availability of second line drugs and the use of drug susceptibility testing results for the treatment of TB in 4675 health care facilities in 12 provinces. The various TB treatment regimens used in 6 different TB hospitals in China are also investigated.

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).

Chapter 8 contains a general discussion of the key findings described in this thesis and addresses some of the methodological issues encountered as well as providing suggestions for future research and MDR-TB control policy.
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**INTRODUCTION**


