Chapter 10
Drug-Resistant TB

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10.1 The Rise of Drug-Resistant Tuberculosis

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

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

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

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

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

10.1.1 The Chinese DR-TB Epidemic

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

10.1.2 Development of Drug Resistance

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

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

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

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

10.1.2.1 Treatment Failures Leading to DR-TB

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

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

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

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

10.1.3 Transmission of DR-TB

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

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

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

10.1.3.1 Transmission Risk Factors

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

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

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

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

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

10.1.3.2 Host Factors

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

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

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

10.2 DR-TB Control Strategy

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

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

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

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

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

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

10.3 DR-TB Mortality

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

10.3.1 DR-TB Will Cost More Social Resources

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

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

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

10.3.2 Measures to Avoid the Occurrence of DR-TB

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

10.3.3 DR-TB: A Global Public Health Threat

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

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

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

10.3.3.1 Hazards DR-TB Poses to Human Health

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

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

10.4 Identification and Diagnosis of DR-TB

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

10.4.1 DR-TB Patient Diagnostic Strategy

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

10.4.1.1 Evaluations of Drug-Resistant TB Diagnostic Techniques and Methods

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

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

10.4.1.2 Sequence of Susceptibility Testing

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

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

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

10.5 Treatment of Patients with DR-TB

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

10.5.1 Chemotherapy

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

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

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

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

10.5.2 The Prognosis of Patients with DR-TB

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

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

10.5.3 Patient Care and Support

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

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

10.5.4 Infection Control in Patients

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

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

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

10.5.5 Quality and Supply of Drugs

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

10.6 Future Trend of Drug-Resistant TB

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

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

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

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

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

10.7 The Urgent Need for New Treatment Medicines

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

10.7.1 Sharp Increase in DR-TB

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

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

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

10.7.2 HIV Dual Infection with M. tuberculosis

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

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

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

10.7.3 Treatment of Latent TB Infection

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

10.7.4 Treatment of Childhood TB

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

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

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