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Multi-drug Resistant (MDR) and Extensively Drug Resistant (XDR) Tuberculosis Case Study Book Project

By

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Global Health

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Multi-drug Resistant (MDR) and Extensively Drug Resistant (XDR) Tuberculosis Case Study Book Project

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An abstract of

A thesis submitted to the Faculty of the
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Multi-drug Resistant (MDR) and Extensively Drug Resistant (XDR) Tuberculosis Case Study Book Project

By Richmond Darko

Background: Multidrug-resistant tuberculosis (MDR TB) is caused by infection with an *M. tuberculosis* isolate resistant to at least Isoniazid (INH) and Rifampin (RIF), the two most potent anti-TB medications. Extensively drug-resistant TB (XDR TB) is a form of TB caused by *M. tuberculosis* isolate resistant) to INH and RIF, and, in addition, a fluoroquinolone and one of three second-line anti-TB injectable drugs. The morbidity, mortality and cost associated with drug-resistant TB is significant and challenges TB control programs throughout the world. Several factors drive the amplification and transmission of drug-resistant TB, including the lack of expertise for complex issues in clinical care and management. This lack of expertise can be addressed through training and education.

Objectives: The objective of this thesis is to provide the scientific background for an MDR TB Case Study Book to be published by the Centers for Disease Control and Prevention (CDC). The objectives of the MDR TB Case Study Book (TCSB) are the following: 1) develop a summary of expert opinions in diagnosing, treating, and managing MDR TB cases in a case study format using actual cases from treatment centers in the United States, 2) present radiographic manifestations of TB for the training and educating of care providers, and 3) provide continuing education (CME) credits through a self-study format.

Methods: Cases were collected from the four TB *Regional Training and Medical Consultation Centers* (*RTMCCs*). Data were extracted from patients' medical records. Each case was written in a format detailing patient's background, disease and management timeline, discussion with expert opinions, and 3 or more self-study questions.

Results: Twenty cases were compiled, 10 are being reviewed by the stakeholders from the RTMCCs and the CDC. Prior to publication of the final product, the book will be piloted among physicians and other public health professionals who specialize in TB treatment and management.

Discussion: A survey of those who read the TCSB and take the CME question will help evaluate the impact of the book on provider knowledge.

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Chapter 1

Introduction and Project Narrative

Multidrug-resistant tuberculosis (MDR TB) is caused by infection with an *M. tuberculosis* isolate resistant to at least Isoniazid (INH) and Rifampin (RIF), the two most potent anti-TB medications. Extensively drug-resistant TB (XDR TB) is a form of TB caused by an *M. tuberculosis* isolate resistant to INH and RIF (i.e. MDR TB), and, in addition, a fluoroquinolone and one of three second-line anti-TB injectable drugs: amikacin, kanamycin or capreomycin. The morbidity, mortality and cost associated with drug-resistant TB is significant and challenges TB control programs throughout the world. Several, factors drive the amplification and transmission of drug-resistant TB, namely, immigration from endemic regions of the world, HIV co-infection, urban crowding, suboptimal institutional infection control measures, lack of resources, patient non-adherence to prescribed drug regimen, lack of coordination between public-private sector, and a lack of expertise for handling the many complex issues in clinical care and management. In resource rich settings, as the institutional memory of TB fades, there is a need for ongoing training and education of health care professionals. There is a shortage of comprehensive TB training and educational products for clinicians that address medical, epidemiologic and case management principles. Furthermore, there is limited literature and evidence-based data on best practices for the care and management of multidrug-resistant TB and extensively drug resistant TB.

In 2005, after needs assessment revealed a gap in expert consultation for managing MDR and XDR TB cases, the MDR TB expert network group, a forum for discussing challenging, drug-resistant TB cases, was established. Since 2005, national case conferences have been held

every two months to discuss challenging cases, seek expert opinion, and present a summary of the literature pertaining to one or two of the key questions raised by the case(s). In 2009, the current project for the development of a case studies module book, based on the MDR expert network meetings (ENM), was proposed. This book will showcase a series of complicated MDR TB and XDR TB cases originally presented at MDR TB ENM. The case study module will provide a summary of the expert opinion on diagnosis, treatment, and management of these cases and provide an opportunity for health care providers to obtain continuing education credits.

Additionally, radiographs (chest-radiographs, computed tomography, and magnetic resonance imaging) will be included, where appropriate, with each case study, to teach clinicians about the radiographic presentation of pulmonary and extrapulmonary TB. The overarching objectives of the project are the following 1) develop a summary of expert opinions in diagnosing, treating, and managing multi-drug resistant TB cases in a case study format using actual cases from treatment centers in the United States, 2) present radiographic manifestations of TB for the training and educating of care providers, and 3) provide continuing education credits through the self-study format. With these objectives, we aim to increase provider knowledge about drug-resistant TB diagnosis, treatment and case management and to improve outcomes for individuals with MDR TB. In all, twenty cases are being compiled and reviewed by the stakeholders from four TB *Regional Training and Medical Consultation Centers* (*RTMCC*) and the Centers for Disease Control and Prevention (CDC). A background review of MDR TB and XDR TB, this thesis, an initial draft, is being written, and will be presented with the cases in a casebook format. Prior to publication of the final product, the book will be piloted among physicians and other public health providers who specialize in the treatment of TB.

Chapter 2

Global Burden of Multi-drug Resistant (MDR) and Extensively Drug Resistant (XDR) Tuberculosis (TB)

Part One

Introduction: MDR and XDR TB:

MDR TB is caused by infection with an *M. tuberculosis* isolate resistant to at least Isoniazid (INH) and Rifampin (RIF), the two most potent anti-TB medications. MDR TB may result from primary infection with already drug-resistant bacteria or form the acquisition and amplification of resistance during the course of a patient's treatment. Extensively drug-resistant TB (XDR TB) is a form of TB caused by an *M. tuberculosis* isolate resistant to INH and RIF (i.e. MDR TB), and, in addition, a fluoroquinolone and one of three second-line anti-TB injectable drugs (amikacin, kanamycin or capreomycin)(WHO 2010).

Epidemiology

According to WHO reports, the proportion of MDR TB among new TB cases reported globally in 2008 ranged from 0% to 28.3%. Since 2000, no country outside the geographic borders of Eastern Europe and Central Asia has reported proportions of MDR TB among new cases exceeding six percent. Almost half of all global MDR TB cases are estimated to have occurred in China and India. In 2008, MDR TB caused an estimated 150,000 deaths worldwide (WHO 2010). The highest incidence rate of MDR TB are found in Eastern European and Central Asian countries, reflecting the slow progress made in Eastern European and Central Asian countries in reaching the Millennium Development Goal target of halving TB mortality rates by 2015 (WHO 2010).

As reported by the WHO, the estimated global number of incident MDR TB episodes among *new* and *relapse* TB cases in 2008 was between 310,000 and 430,000 episodes (best estimate at 360,000). MDR TB cases may have been infected with an MDR strain of TB to begin with, i.e. a primary MDR TB disease, or may occur in a previously treated TB case suggesting acquired MDR during the course of treatment. The estimated global number of incident *acquired* MDR TB was between 83,000 and 110,000 episodes (best estimate, 94 000)(WHO 2010). The number of prevalent cases of MDR TB in many parts of the world is estimated to be significantly higher than the number arising annually (WHO 2010).

Mortality from MDR-TB

An estimated 150,000 deaths caused by MDR TB occurred globally in 2008, including those with co-infected with Human Immunodeficiency (HIV) (range: 53,000–270 000). Further, the estimated number of MDR TB deaths excluding those with HIV infection was 97,000 (range: 6000–220 000)(WHO 2010).

Growing Need for Continuous Surveillance:

Since 1994, only 59% of all countries have been able to collect data on drug resistance at the subnational or national level. The WHO continues to stress the urgent need to obtain information, especially from Africa, South Asia, and Eastern Europe and those high MDR TB burden nations where data have never been reported according to WHO guidelines, namely Bangladesh, Belarus, Kyrgyzstan, Pakistan and Nigeria.

Of the 72 countries that conducted drug resistance surveys between 1994 and 2009, more than one third collected data only at the subnational level (state, provincial or district) and or have data that are older than 10 years (that is, surveys that were conducted before 2000). The WHO reports that less than one fourth of all countries (22%), the vast majority of whom are

high-income countries, have continuous surveillance mechanisms in place. Not a single low-income country, and no country in the African Region (with the exception of South Africa) and no nation in the Southeast Asia, has a continuous drug resistance surveillance in place(WHO 2010).

It warrants repeating that countries, especially the high TB-burdened nations, need to expand the scope of their surveillance by adopting systematic and continuous surveillance strategies that cover entire populations in order to monitor trends in the emergence of drug resistance amongst its populations. The most commonly cited challenge that hinders nations who do not currently have a surveillance mechanism is cost. Adopting and maintaining a continuous national surveillance system is not an inexpensive undertaking. Given the challenges and costs of establishing continuous surveillance of drug resistance, many countries only have the capacity for periodic surveys of a representative sample of patients.

A handful of high MDR TB burden countries – including Belarus, Bulgaria, Kazakhstan, the Russian Federation, Georgia, the Republic of Moldova and South Africa have surveillance mechanisms that, with additional capacity strengthening, could soon provide high-quality nationwide drug resistance data. These countries may serve as models in the global effort to improve surveillance mechanisms beyond the developed world(WHO 2010).

Control Strategies

Controlling the morbidity and mortality of MDR TB requires a clear understanding of what factors put people at risk of developing the disease. There are several factors associated with MDR TB. These factors exist at two broad levels: 1. the individual level and 2. the community or population level. It has been observed that MDR TB emerges at an appreciably high rate among previously treated TB patients and among patients who are HIV positive.

Furthermore, MDR TB has been observed to occur at disproportionately higher levels among people of a certain age-group, or sex (Suchindran, Brouwer et al. 2009). All these factors, among others, prompt the need to analyze MDR TB by sub-categories that may also be perceived as risk factors for the disease. In this section, we will highlight some of the risk factors for emergence of MDR-TB at the community/population level (we will subsequently discuss the individual risk factors under the "Treatment" section).

At the population level, there are identifiable factors commonly associated with selection of resistance and generation of MDR TB. These include not correctly implementing directly observed therapy short-course (DOTS) (detailed below) and DOTS expansion strategies, as well as the inadequate supply or poor quality of anti-TB drugs and social and political instability. Non-implementation of DOTS and expansion strategies may stem from poor organization and funding for well-functioning national TB programs, inadequate or absent national DOTS guidelines, inadequate or very limited staff training or as is often seen, non-standardized monitoring by DOTS staff. Additional factors include poor infection control in health facilities, high regional rates of HIV infection, and high regional prevalence of highly virulent multi-drug resistant strains of *M. tuberculosis* (Caminero 2010).

Disease prevention is a dogma central to the study and practice of public health. Central to MDR TB prevention efforts are strategies meant to stop the occurrence of *drug sensitive* TB. In 1994 for example, the World Health Organization declared TB a global emergency. The WHO consequently introduced the DOTS strategy for global TB control. DOTS remains at the heart of the WHO "Stop TB Program", and has played a central role in the effort to control TB morbidity and mortality. The DOTS strategy is designed around five essential activities: (1) case detection by sputum smear microscopy among symptomatic patients that voluntarily report to health services, (2) directly observed therapy using standard short-course regimens, (3) regular supply

of medication, (4) governmental commitment to sustained TB control by providing resources and infrastructural capacity, and (5) a standardized recording and reporting system that allows assessment of individual treatment results and of the TB control program overall (Böttger and Springer 2007). Despite the introduction of DOTS, the global burden of TB still remains at alarming levels. Even in areas where DOTS strategies are implemented, there have been successes and failures. Some have argued that the failure of the DOTS strategy to control TB results from failure of adequate implementation, poor public health infrastructure, and general poverty (Whalen 2006). It is important to note, however, that DOTS, as a treatment and prevention program, is ideally combined with components that actively target transmission, for example, a program that is designed to interrupt the spread of *M .tuberculosis* in the community by focusing on early and effective diagnosis and by implementing active case detection mechanisms (Grandjean and Moore 2008).

Advances in Diagnosis and Case Detection of MDR TB

For over a century, sputum smear microscopy has been the cornerstone of TB diagnosis and case detection. In the industrialized world, sputum culture and (if positive) drug sensitivity tests (DST) are now the standard of care. However, a great majority of TB cases worldwide are diagnosed only by sputum smear microscopy (Grandjean and Moore 2008). In much of the developing world, however, there is limited ability to perform and/or standardization of DST. Access to DST is increasingly important in the era of emerging MDR and XDR TB. This threatens to push TB control into a 'post-antibiotic era,' where there are no effective therapies (Raviglione 2006). In disease control, there are other factors that are as important as having good laboratory testing; these include sustainable human resources, sample transport, bio-safety, information systems, and laboratory maintenance. In resource-limited, high-burden settings, considerable

energy has been directed in recent years towards development of improved TB and MDR TB diagnostics suitable to the realities of the respective setting (WHO 2010). Market potential has encouraged commercial interest (Perkins 2006); non-proprietary methodologies have also emerged (Cunningham and Perkins 2006), (WHO 2006).

Despite some progress in improving diagnostic modalities, MDR and XDR TB continue to be diagnosed at the level of the national/regional reference laboratory rather than at the district hospital in many resource-limited settings. Although it appears impractical to apply models streamlined in resource-rich settings to the resource-limited countries, it is possible, even in those regions with limited resources, to strategically and quickly diagnose MDR TB and streamline samples from these patients for rapid second-line drug susceptibility testing (Grandjean and Moore 2008).

Prior to recommending a broad use of a diagnostic tests in resource-limited, high-burden settings, the proposed test must be proven to be rapid, simple, reliable, cost-effective and easy to establish and maintain without compromising bio-safety. Preferably, the test should be performed as close to the point of care as possible to minimize delays in transport of samples and results to and from reference laboratories. These essential requirements continue to challenge new test development and recommendation efforts.

Laboratory functions are a fundamental aspect of national TB control programs (NTP's). In TB diagnosis, laboratory services and mycobacteriology go hand in hand. However, TB laboratory services are often neglected components of national TB control programs. There is a growing need to upgrade existing laboratory services and strengthen capacity to perform culture and drug susceptibility testing. Furthermore, a major pitfall of the current diagnostic tests for MDR and XDR TB has been that it may take up to three months to obtain results of drug

sensitivity tests. During this time, a patient may be receiving inappropriate chemotherapy, resistance may become amplified, and resistance strains may continue to spread.

In a large, multi-country study, Boehme et al. evaluated a fully automated rapid tuberculosis test (XpertMTB/RIF) for the presence of *Mycobacterium tuberculosis* and resistance to rifampin (RIF) on selected TB patients in Peru, Azerbaijan, South Africa and India. With a single test, this assay identified 98% of patients with smear-positive as well as culture-positive TB (including more than 70% of patients with smear-negative and culture-positive disease) and correctly identified 98% of bacteria that were resistant to rifampin. The MTB/RIF test provided sensitive detection of TB and was able to detect resistance to rifampin from untreated sputum in less than two hours with minimal hands-on time(Small and Pai 2010), (Boehme, Nabeta et al. 2010). The MTB/RIF assay is simple to perform with minimal training; it is not susceptible to cross-contamination, and requires minimal bio-safety facilities, a feature that proves useful in resource-limited settings. Further, it has a high sensitivity in smear-negative TB, a feature particularly relevant in HIV infected patients (Small and Pai 2010).

In 2010, following review of the scientific evidence, through an Expert Group and the WHO's Strategic and Technical Advisory Group for Tuberculosis, the WHO endorsed the rapid diagnostic test (XpertMTB/RIF). The WHO subsequently *strongly recommended* that the automated rapid DNA test be used as the initial diagnostic test in individuals suspected of MDR TB or HIV/TB. They also made the following *conditional recommendation*: the new automated DNA test may be used as a follow-on test to microscopy in settings where MDR TB and or HIV are of lesser concern, especially in smear-negative specimens (recognizing major resource implications). Through its technical partners, the WHO also encouraged national TB programs worldwide to seek additional resources from the Global Fund in support of the adoption of the new TB test (WHO 2010). Recent work has shown that the MTB/RIF test can effectively be used

in low-resource settings to simplify patients' access to early and accurate diagnosis, thereby potentially decreasing morbidity associated with diagnostic delay, dropout and mistreatment (Boehme, Nicol et al. 2011). More remains to be learned about the degree of integration of the new test into national TB programs and the level of impact any such adoption will have on strengthening the global capacity to diagnose MDR TB and HIV/TB.

Part Two

TB and HIV

For several years now, experts have believed that there is an association between HIV infection and MDR TB. However, the association between HIV infection and MDR-TB has not yet been fully investigated. A systematic review and meta-analysis by Suchindran et al summarizes the evidence on the association between HIV infection and MDR TB (Suchindran, Brouwer et al. 2009). The authors' review of the current literature demonstrates an overall association between MDR TB and HIV or acquired MDR TB and HIV. The report does not fully clarify the relationship between MDR TB and HIV infection. Lawn and Churchyard also argue there is critical overlap between HIV and global multidrug-resistant TB epidemics. They agree that while it is unclear whether HIV is driving a disproportionate increase in multidrug-resistant TB cases at a population level, HIV has nevertheless been a potent risk factor for institutional outbreaks, especially in South Africa and eastern Europe (Lawn and Churchyard 2009).

The risk factors for developing MDR TB can be categorized as either individual or group (population) risk. Regardless of whether HIV infection itself is an independent risk factor for the development of MDR-TB at the individual level, the increase in the cluster of immunocompromised patients serving as both hosts and vectors for all forms of TB, including MDR TB and XDR TB, is likely to raise the absolute burden of drug-resistant TB at the

population level. Furthermore, at the programmatic level, the HIV epidemic has overwhelmed and continues to disrupt established (and previously successful) TB-control programs, causing increases in treatment failure rates and increasing the opportunity for drug-resistant TB to emerge and spread among both HIV-infected and uninfected persons worldwide (Andrews, Shah et al. 2007).

An estimated 1.37 million new cases of HIV/TB occurred in 2007, representing 15% of the total global burden of TB. Furthermore, an estimated 456,000 HIV/TB deaths accounted for 23% of global HIV/AIDS mortality. Sub-Saharan Africa was the worst affected region with 79% of the disease burden. The epicenter of the what can be referred to as the co-epidemic of HIV and MDR TB lies in the south of the continent, with South Africa alone accounting for over one quarter of all cases in 2007 (Lawn and Churchyard 2009).

Table 1: HIV-associated Multidrug-resistant TB outbreaks in the industrialized world (Wells, Cegielski et al. 2007)[a]

	Patient with MDR TB		
Location, date	Total No.	**%HIV+**	% Died
Hospital(Florida),1988-1990	65	**93**	72
Hospital (New York City), 1989-1990	51	**100**	89
Hospital (New York City), 1990-1991	70	**95**	77
Hospital (New York City), 1991-1992	32	**91**	83
Two Hospitals in Italy, 1991-1995	116	**98**	95
Hospital (Madrid, Spain) 1991-1995	48	**100**	98
Hospital (Buenos Aires, Argentina) 1994-1995	68	**100**	93
Prison System (New York State)	42	**98**	79

[a] Illustrates a high HIV incidence and mortality among reported MDR TB patients from several institutions

HIV-associated TB mortality

Though the link between HIV infection and TB is not clear, patients with HIV/TB have high mortality risk regardless of whether HIV infection is an independent risk factor for developing MDR-TB (Lawn and Churchyard 2009). It is clear that HIV positive patients with MDR or XDR TB have high mortality rate (Kvasnovsky, Cegielski et al. 2011). Indeed, TB is a leading cause of death in HIV-infected patients in TB endemic countries, including those with free access to anti-retroviral therapy (ART) such as in Brazil. The WHO estimated that there were a total of 456,000 HIV/TB deaths in 2007, accounting for 33% of the number of incident HIV/TB cases that year. Moreover, the HIV/TB deaths represented 23% of the estimated 2 million deaths from HIV/AIDS in 2007(Lawn and Churchyard 2009).

Part Three

Biologic Basis and Mechanism of Resistance in MDR and XDR TB

By definition, MDR TB is caused by bacteria resistant to INH and rifampicin. MDR TB results from primary infection with resistant bacteria but resistance may also develop in the course of a patient's treatment. Understanding the mechanisms of mycobacterial resistance to the anti-TB drugs will enable the development of more rapid molecular diagnostic tests. Learning more about mycobacteria will also generate implications for designing new anti-TB drugs and assist the implementation of measures to prevent the development of such resistance(Zhang and Yew 2009), (Zhang 2005).

In 1945, the first anti-TB drug, streptomycin, was developed(Shenoi and Friedland 2009), (Schatz, Bugie et al. 2005). *Mycobacterium tuberculosis* strains that were resistant to streptomycin(SM) appeared soon after the introduction of the drug for treatment of

TB(Brit_Med_Council 1948). By 1947,resistance to this drug was already noted and it soon became necessary to use multiple-drug regimens to treat TB (Shenoi and Friedland 2009).

With respect to the TB patient, the development of drug resistance is often understood to be of two general categories: primary and acquired. Resistance in *Mycobacterium tuberculosis* arises from spontaneous chromosomal mutations at low frequency. Resistance occurring in a previously treated TB patient is referred to as acquired resistance (Chan and Iseman 2008). Primary resistance occurs when the resistant *M. tuberculosis* strain is transmitted to a new host, as it causes TB that is already resistant to the indicated drug(s) (Ahmad and Mokaddas 2009). The definitions of "primary" and "acquired" drug resistance are often subject to misclassification when previous treatment cannot be verified for a given patient. As such, the term "initial drug resistance" is often preferred to "primary drug resistance" (Zhang and Yew 2009).

Genetic resistance to an anti-TB drug results from spontaneous chromosomal mutations that occur at a predictable frequency of 10^{-6} to 10^{-8}mycobacterial replications. Mobile genetic elements such as plasmids and transposons, which are known to mediate drug resistance in various bacterial species, do not play a role in *M. tuberculosis* resistance development. Because the mutations resulting in drug resistance are unlinked, the probability of developing resistance to three drugs used simultaneously becomes $10^{-18}$to 10^{-20} (Zhang and Yew 2009), a very rare occurrence, highlighting the essential need to treat TB with multiple drugs. Accumulation of sequential mutations and amplification of the spontaneous genetic mutations through human error results in clinically drug-resistant TB. These errors often include monotherapy (using only a single drug for TB treatment) due to irregular drug supply, inappropriate physician prescription, poor patient adherence to treatment, and programmatic inefficiencies (Jain and Dixit 2008). Subsequent transmission of resistant *M. tuberculosis* strains from the index patient to others (who are previously uninfected with resistant strains) further complicates the issue.

Drug-specific molecular mechanisms of drug resistance have been elucidated for the major first- and second-line drugs rifampicin, isoniazid, pyrazinamide, ethambutol, the aminoglycosides and the fluoroquinolones (Zhang and Yew 2009).

We will now proceed to highlight a few of these drug-specific resistance mechanisms. For a more detailed review of the mechanisms of resistance in *M. tuberculosis*, the reader may refer to the article by Zhang and Yew (Zhang and Yew 2009).

Isoniazid (INH)

Since its discovery in 1952, isoniazid is the most widely used first-line anti-TB drug and has been at the helm of all effective chemotherapeutic regimens for the treatment of TB disease and latent infection. While *M. tuberculosis* is highly susceptible to INH, isoniazid is only active against growing bacteria and is not active against non-replicating bacilli or under anaerobic conditions (Zhang and Yew 2009). INH is a pro-drug and is converted to its active form by the catalase peroxidase enzyme (KatG) encoded by the *kat*G gene (Zhang and Yew 2009), (Zhang, Heym et al. 1992). The primary target of INH inhibitions is thought to be the InhA enzyme (enoyl-acylcarrier protein reductase), involved in elongation of fatty acids in mycolic acid synthesis (Zhang and Yew 2009), (Banerjee, Dubnau et al. 1994). There is a higher frequency of resistance to INH than is the case for the other anti-TB drugs. Resistance to INH occurs at a frequency of 10^{-5} to 10^{-6} bacilli in vitro. KatG S315T mutation is the most common mutation found in INH-resistant strains, and accounts for 50–95% of INH-resistant clinical isolates (Cole 2005), (Zhang and Yew 2009). Resistance to INH has also been shown to occur via mutations in the promoter region of *mab*A/*inh*A operon, causing an over-expression of InhA. Nevertheless, approximately 10–25% of low-level INH-resistant strains do not have mutations in *kat*G or *inh*A, which may be due to new mechanism(s) of resistance not yet elucidated (Zhang and Yew 2009).

Rifampicin (RMP) or Rifampin (RIF)

RMP is bactericidal for *M. tuberculosis* and has activity against both growing and stationary phase bacilli with low metabolic activity(Zhang and Yew 2009). It has a high destructive activity in vivo, which explains its ability to truncate TB treatment from 12–18 months to 9 months (Vilcheze, Av-Gay et al. 2008). The antibiotic activity of RMP involves its ability to interfere with RNA synthesis by binding to the βsubunit of the bacterial RNA polymerase.

Resistance in *M. tuberculosis* to RMP occurs at a frequency of $10^{-7}$to 10^{-8} (Zhang and Yew 2009). Mutations in a defined region of the 81 base pair (bp) region of the *rpo*B are present in about 96% of RMP-resistant *M. tuberculosis* isolates (Telenti, Imboden et al. 1993).

Pyrazinamide (PZA)

PZA is used in combination with INH and RMP (Caminero 2006) and is only active against *M. tuberculosis* in an acidic environment (e.g., pH=5.5) (Zhang and Yew 2009). PZA plays a unique role in shortening TB treatment from the previous 9–12 months to 6 months by killing the population of remaining bacilli in acidic pH environment in the lesions that is not killed by the other drugs (Mitnick, McGee et al. 2009). It is also a pro-drug and as such requires conversion to its active form, pyrazinoic acid (POA), by the pyrazinamidase/ nicotinamidase enzyme encoded by the *pnc*A gene of *M. tuberculosis* (Scorpio and Zhang 1996). PZA-resistant *M. tuberculosis* strains lose pyrazinamidase/nicotinamidase activity with most of these strains (72–97%) having mutations in *pnc*A (Zhang and Yew 2009). Lastly, PZA is active only against *M. tuberculosis* complex organisms (*M. tuberculosis, M. africanum* and *M. microti*), but not *M. bovis* due to a characteristic mutation in its *pnc*A gene (Scorpio and Zhang 1996).

Ethambutol (EMB)

EMB [(*S,S*)-2,2′(ethylenediimino)di-1-butanol] is a first-line drug used in combination with INH, RMP, and PZA to prevent the emergence of drug resistance (Mitnick, McGee et al. 2009). EMB is a bacteriostatic agent that is active for growing bacilli and has no effect on non-replicating bacilli (Zhang and Yew 2009). EMB interferes with the biosynthesis of cell wall arabinogalactan (Zhang and Yew 2009), (Takayama and Kilburn 1989). The drug interferes with the polymerization of cell-wall arabinan of arabinogalactan and of lipoarabinomannan, inducing the accumulation of D-arabinofuranosyl-P-decaprenol, an intermediate in arabinan biosynthesis. Mutation to EMB resistance occurs at a frequency of10^{-5}. Mutations in the *emb*CAB operon, in particular *emb*B, and occasionally *emb*C, are responsible for resistance to EMB (Zhang and Yew 2009), (Telenti, Philipp et al. 1997). The *emb*B codon 306 mutation in, most common in EMB-resistant bacterial isolates, account s for as high as 68% resistant strains (Zhang and Yew 2009), (Sreevatsan, Stockbauer et al. 1997). Approximately 35% of EMB-resistant strains do not have *emb*B mutations, which implies there may be other mechanisms of EMB resistance (Zhang and Yew 2009).

Aminoglycosides (streptomycin (SM), kanamycin (KM), amikacin (AMK), capreomycin (CPM)

Streptomycin is an aminoglycoside antibiotic that kills actively growing bacteria, but is inactive against non-growing or intracellular bacilli. The drug inhibits protein synthesis by binding to the 30S subunit of bacterial ribosome, causing misreading of the mRNA message during translation (Zhang and Yew 2009), (Honore and Cole 1994). The site of action of SM is the 30S subunit of the ribosome at the ribosomal protein S12 and the 16S rRNA. Resistance to SM is caused by mutations in the S12 protein encoded by *rps*L gene and 16S rRNA encoded by *rrs* gene

(Zhang and Yew 2009), but, about 20–30% of SM-resistant strains with a low level of resistance do not have mutations in *rps*L or *rrs* (Zhang and Yew 2009), (Cooksey, Morlock et al. 1996). Kanamycin (KM) and its derivative amikacin (AMK) are also inhibitors of protein synthesis through modification of ribosomal structures at the 16S rRNA, which partly explains why variable cross-resistance may be observed between KM, AMK, CPM or viomycin (VM) (Zhang and Yew 2009). Furthermore, multiple mutations may occur in the *rrs* gene in one strain, thus creating cross-resistance among these agents (Maus, Plikaytis et al. 2005). SM resistant strains are usually still susceptible to KM and AMK (Zhang and Yew 2009).

Fluoroquinolones (FQs)

A fifth drug-specific resistance mechanism are fluoroquinolones (FQs) which functionally inhibit DNA gyrase (topoisomerase II and topoisomerase IV) resulting in microbial death. DNA topoisomerases are a group of enzymes responsible for keeping chromosomes in a morphological state that is essential for cellular function. In the cell, topoisomerases regulate DNA supercoiling and unlink tangled nucleic acid strands in order to allow DNA replication to occur (Tsai and Lieber 2010). *M. tuberculosis* has *gyr*A and *gyr*B encoding its DNA gyrase subunits (Zhang and Yew 2009). Mutations at specific regions on *gyr*A (320 bp) and *gyr*B (375 bp), are believed to be the most important areas involved in the exhibition of FQ resistance in *M. tuberculosis* (Takiff, Salazar et al. 1994), (Zhang and Yew 2009). There are other mechanisms thought to be responsible for the mycobacterial resistance to FQs, namely, decreased cell-wall permeability to the drug, drug efflux pump, drug sequestration, or drug inactivation (Drlica and Malik 2003). Several other alternative resistance mechanisms have been proposed and discussed elsewhere (Zhang and Yew 2009).

Ethionamide (ETH) /prothionamide and thioamides

Lastly, ETH (2-ethylisonicotinamide) is a derivative of isonicotinic acid, and like INH, is a pro-drug that is activated by EtaA/EthA (a monooxygenase). ETH inhibits the same cellular target as INH, the InhA of the mycolic acid synthesis pathway (Zhang and Yew 2009). Prothionamide (PTH, 2-ethyl-4-pyridinecarbothioamide) shares structure and activity almost identical to that of ETH. Mutations in the drug-activating enzyme EtaA/EthA cause resistance to ETH and other thioamides. In addition, mutations in the target InhA confer resistance to both ETH and INH (Zhang and Yew 2009).

Part Four

Management Options

Drug Therapy against MDR and XDR TB

In 1946, after the discovery of streptomycin, the British Medical Research Council began a randomized clinical trial. The results showed efficacy of streptomycin against TB (Mitchison 2005). In 1948 Bradford Hill recorded that although two thirds of patients with advanced pulmonary TB showed symptomatic improvement with streptomycin monotherapy. Within six months, 35 of 41 patients had developed streptomycin resistance (Brit_Med_Council 1948), (Grant, Gothard et al. 2008). This marked the beginning of the use of combination therapy as standard treatment for TB. Subsequently, combining streptomycin with isoniazid and para-aminosalicylic acid controlled the development of resistant bacilli, but treatment for up to two years was often required. Clinical trials from 1970 using combination therapy that included rifampicin showed that the treatment could safely be shortened to six months (Grant, Gothard et al. 2008), (Mitchison 2005). Historically, the initial regimens for the treatment of TB were defined

by what was available in the middle of the 20th century, namely, streptomycin, para-aminosalicylic acid, and isoniazid. As new drugs were developed, they were tested with older drugs until the current regimen of isoniazid, rifampin, and pyrazinamide (often with ethambutol as a fourth drug) was defined (Mitnick, McGee et al. 2009). Unfortunately, and for many reasons (previously discussed), the emergence of drug resistance and the options available for the management of drug-resistant TB remain a global challenge. To date, few data are available from randomized controlled trials to guide treatment of drug resistant TB, and none for multidrug resistant TB. As such, most of the information available concerning the treatment of TB, especially MDR TB, are based on observational epidemiological studies and on national and international guidelines (Grant, Gothard et al. 2008).

M. tuberculosis is metabolically classified into two subpopulations: those bacteria that are metabolically active and replicating, and those that are not (Mitnick, McGee et al. 2009). In this sense, successful treatment regimens typically contain drug components that act on both subpopulations. Persisting organisms are metabolically dormant and do not actively replicate. Thus, their elimination requires prolonged treatment duration. The ability of drugs to kill these persisting mycobacteria is termed *sterilizing activity* (Mitnick, McGee et al. 2009). Drugs with high sterilizing activity contribute significantly to reducing the duration of therapy. The focus of current efforts is to find regimens with such potency to destroy persisting organisms or prevent *persisters* from forming and in so doing significantly shortening duration of treatment. Prolonged treatment duration cost patients and programs a great deal of money; in resource-limited nations, 9-month regimens significantly tax already overburdened heath systems (Mitnick, McGee et al. 2009). The most advanced clinical and programmatic development efforts are concentrated on MDR and XDR TB. Currently, only relatively weak regimens are available for disease caused by the resistant strains of TB, and treatment generally lasts 2 years or more,

curing approximately 70% of patients(Mitnick, McGee et al. 2009). New chemotherapeutic agents must improve probability of cure and/or reduce the duration of treatment for MDR and XDR TB. In combination with selected first-line agents, the new TB drugs ought to produce extremely short course regimens with few side effects, further revolutionizing the treatment of TB(Mitnick, McGee et al. 2009).

The remainder of this section will address issues regarding prevention of MDR and XDR TB, disease management, treatment outcomes, new advanced drugs that aid therapeutic efforts, vaccine development and further needs in the effort to wrangle the global burden of MDR- and XDR TB.

Prevention of MDR and XDR TB

If pressed to propose one mechanism through which we can effectively reduce the morbidity and mortality of MDR and XDR TB, the timely diagnosis and appropriate treatment of drug-sensitive TB would undoubtedly be central to any such mechanism.

The Centers for Disease Control and Prevention (CDC) statements and guidelines (1990 and 1994) for preventing transmission of TB, included: (i) prompt isolation and treatment of patients with TB; (ii) rapid diagnostic techniques for processing specimens containing *M. tuberculosis*; (iii) negative-pressure ventilation rooms for isolation; and (iv) appropriate masks/ respirators for health-care workers (Yew and Leung 2007), (Maloney, Pearson et al. 1995). The CDC guidelines were updated in 2005 with changes made according to the pertinent shifts in the epidemiology of the disease, advances in scientific understanding, and changes in the scope of healthcare settings and infection screening patterns. Nevertheless, central to the guidelines remains the issue of prevention of disease transmission (Yew and Leung 2007), (Jensen, Lambert et al. 2005). The CDC, in collaboration with federal agencies and international partners, has also

taken on the followings tasks in its efforts to prevent MDR and (specifically) XDR TB both in the United States and globally: (i) strengthening TB services for people living with HIV/AIDS, (ii) assembling response teams to help countries and WHO teams during an outbreak, (iii) improving access to TB drugs through support of the Global Fund, (iv) developing international TB testing standards, (v) building capacity of health care providers, (vi) reconvening the Federal TB Task Force originally built in the 1990s to tackle the emergence of MDR TB, (vii) providing technical assistance to expand program capacity in host countries, and (viii) supporting TB communication and education efforts(CDC 2010).

Diagnosis of MDR and XDR TB

The importance of reliable, quick, simple and cost-effective diagnostic tools for management of MDR-TB cannot be overemphasized, and arriving at such tools remains a challenge in the collective efforts to control MDR TB. The first step in diagnosing a disease is suspicion of the disease in the presenting patient. To make diagnosis more cost effective, care providers must build upon the initial suspicion taking into consideration the patient's *risk factors* for MDR TB. To date the major individual risk factor for developing MDR and XDR TB is having had previous treatment for TB (Monedero and Caminero 2010).

Suspecting MDR TB

The suspicion of MDR-TB should occur in the following situations (Prasad 2007): (1) history of contact with known cases of Drug Resistant/MDR TB patients, (2) history of many courses of irregular/regular treatment of (drug-sensitive) TB, (3)radiological deterioration in chest radiograph. This may be a sign of treatment failure and clinical deterioration. Radiographic increase in size of cavities, increase in existing lesions and appearance of new lesion(s) are usually signs of worsening disease. Radiological worsening in addition to positive sputum

and/or clinical worsening should trigger a higher index of suspicion for resistant TB. More suspicion of MDR TB include (4) persistent positive sputum smears for acid fast bacilli (AFB) even after up to five months of WHO retreatment regimens, (5) a fall and rise phenomenon in which sputum smear initially becomes negative and later becomes persistently positive, (6) drug sensitivity test (DST) results indicating resistance to at least isoniazid and rifampicin. Number 6 is, indeed, the gold standard for the diagnosis of MDR TB. However, one has to keep in mind the limitation of highly specific testing, since the technique is complex and difficult to perform accurately even when skilled personnel are available and laboratory facilities are of a high standard. As such, the above reasons for suspicion should not be abandoned in the face of a negative DST result.

Molecular Diagnosis of MDR TB

DST is the gold standard for diagnosing drug resistant TB. DST is the process of determining resistance in specimens by confronting the bacilli with different antibiotics to assess their ability to survive and multiply. DST can be performed in solid or more rapid liquid culture media. Despite its wide use, DST has several critical limitations (Monedero and Caminero 2010), (Kim 2005).To begin with, testing could take anywhere from ten days to two months, which predictably puts considerable time limitations on clinical decision-making. Secondly, DST is expensive and demands specialized technical expertise. Thirdly, in vitro DST frequently shows poor inter-laboratory reproducibility and low correlation with clinical response (Monedero and Caminero 2010). In light of all these limitations, DST results alone should never be used to guide the clinical decision. A complete history of the anti-TB drugs used by the patient and their availability in the country is needed to complement the information given by results of sensitivity test (Monedero and Caminero 2010). Research continues to focus on ways to address

these limitations. New genotypic techniques are being formulated to tackle the current drawbacks associated with DST. Many of these techniques begin by identifying the mutations linked to phenotypic resistance, another reason why understanding mechanisms of mycobacteria resistance is crucial. The main advantage of genotypic methods is that it provides results within 24 hours. In addition, it is relatively economical and identifies resistance with a high level of reliability (Monedero and Caminero 2010), (Richter, Rusch-Gerdes et al. 2009). These new methods promise to address the challenges of coming up with reliable, quick, simple and cost-effective diagnostic tools for drug-resistant TB. The BACTEC method, perhaps the most common rapid technique being used worldwide, is gradually being phased out due in part to radioactivity hazard. Another disadvantage of the BACTEC method is that it often needs continuous, stable electricity to maintain constant incubator temperature, and some expensive reagents have shelf-lives of half a year or less upon arrival (Van Deun, Martin et al. 2010). Several other methods based on non-radioactive detection strategies are under consideration including Mycobacterial Growth Indicator Tube, Septi-Check, PhaB Assay, Alamar Blue Assay, resazurinmicrotiter assay, Luciferase Reporter Phage Assay and E-test (Katoch 2010).

In 2010, the WHO endorsed the rapid diagnostic test (XpertMTB/RIF) and strongly recommended that the automated rapid DNA test be used as the initial diagnostic test in individuals suspected of MDR TB or HIV-TB. The relative rapidity, simplicity and automaticity of the new technique, and the current multi-organizational and multi-national efforts to make the technique more affordable will undoubtedly revolutionize the diagnosis of drug-resistant TB.

Treatment of MDR and XDR TB

A paramount goal of TB treatment is to provide adequate treatment and to prevent the acquisition of drug-resistant TB. If drug-resistant TB (DR TB, referring to any drug resistance) is

present or develops during treatment, it is essential to use an appropriate DR TB regimen (Chiang and Schaaf 2010). The WHO recommends the following three treatment strategies for MDR TB: (1) standardized treatment, (2) standardized treatment followed by individualized treatment and (3) empirical treatment followed by individualized treatment(WHO 2008a). It is important to emphasize the distinction between standardized and individualized treatment. Standardized treatment regimens are based primarily on surveillance data, whereas individualized regimens take into consideration the conditions of the patient (previous history of anti-TB treatment and DST results). The patient's previous history of anti-TB treatment, in combination with the surveillance data, are then used to design an empirical regimen (Chiang and Schaaf 2010). A systematic review by Orenstein and others reported that the outcome of individualized regimens is better than for a standardized regimen (Orenstein, Basu et al. 2009), (Chiang and Schaaf 2010). It is also critical to note that it may not be sufficient to use standardized regimens to treat patients who have previously been exposed to second-line drugs.

When formulating individualized treatment, Chiang and Schaaf delineate the following as vital components (Chiang and Schaaf 2010): (1) having quality-assured DST, (2) short turnaround time for DST, (3) high probability of and ability in obtaining a detailed history of previous anti-TB treatment, (4) being well-trained in the interpretation of DST results, and (5) being competent in designing an MDR TB regimen. Undoubtedly, these underscore the importance of DST in the formulation of individualized care for the TB patient. However, it must also be noted that DST has its limitations, as previously discussed. That is, despite its appreciable superiority, individualized treatment is a demanding approach and prone to inaccuracy if the essential components outlined above are overlooked.

Although the number of drugs required to cure MDR TB is not known, most of the published studies have used 4 to 6 drugs (CNTC 2008). It is recommended that in choosing

drugs, one begins with the available first-line drugs to which the isolate is known to be susceptible, then add a fluoroquinolone and an injectable agent; then add oral second-line drugs to achieve a total of 4 to 6 drugs in the regimen (CNTC 2008). The Francis J. Curry "Drug-Resistant Guide" is a resource for the clinicians when treating these extremely complicated and challenging cases (CNTC 2008).

Monedero and Caminero outline the following as fundamental aspects of the treatment of a patient who is afflicted with drug-resistant TB (Monedero and Caminero 2010):

(A) Diagnose

History of drugs: 1 month of monotherapy or single drug intake over a failure regimen could be a strong predictor of resistance.
DST: most reliable for Rifampin and Isoniazid; also reliable for Kanamycin and Fluoroquinolone; less reliable for Ethambutol and Pyrazinamide; very low reliability for group 4 drugs.

(B) Number of drugs

At least four effective drugs: never used in the past or susceptible by DST taking into account DST reliability and cross-resistance.

(C) Drug selection

Use first line drugs if still effective.
One injectable.
One Fluoroquinolone.
Use group 4 drugs until complete four effective drugs.
If necessary, use group 5 drugs to strengthen the regimen or when four effective drugs are not reached with the previous groups.

(D) Length of the injectable

At least 4 months after smear or culture conversion.
Longer if there aren't three effective drugs during the continuation phase or drugs are from group 5.

(E) Surgery Consider only if:

few effective drugs are available;
localized lesions;
sufficient respiratory reserve.

(E) Ideal regimen

Standardized: if there is no use of second line drugs in the past.
Individualized: use of second line drugs in the past or contact with a multidrug-resistant patient who was treated with them (treat with the effective regimen of the index case).

In the absence of randomized control trials (RCT), no clear guidelines are available for XDR. Furthermore, XDR conditions can be quite different from patient to patient, depending on the pattern of resistance and previous drugs used. In XDR management, because four effective drugs are often not available, the use of multiple drugs (more than six in some settings), lengthy

treatments (often more than 24 to 30 months), lengthy injectable use, surgery and other treatment options have to be considered (Monedero and Caminero 2010).

The Role of Surgery in Managing MDR and XDR TB

Surgery in MDR TB is limited to a few circumstances: They mainly involve cases with fewer than four effective drugs available for treatment (mostly XDR TB), if lesions are isolated and localized, and where there is sufficient respiratory reserve(Monedero and Caminero 2010). There are three primary selection criteria for adjunctive surgery in MDR TB patients. They include: (1) when drug resistance, as revealed by *in vitro* susceptibility testing, is so severe or extensive that there is a high probability of failure or relapse with medical therapy alone (2) disease is sufficiently localized, and imaging studies reveal disease can be resected with expectation of adequate cardiopulmonary capacity post-surgery, and (3) drug activity is sufficient to suppress any remaining mycobacterial burden post-surgery (Yew and Leung 2007).

Prior to surgery the patient should receive at least three months of medical therapy, and be rendered culture-negative if possible. Bilateral disease, it should be noted, does not preclude surgical intervention, unless disease is extremely extensive. According to Yew and Leung, the cure rates could reach 90% with post-surgery chemotherapy, in developed nations. In resource-limited areas, the cure rates might be lower (63–75%), but surgery is still useful as additive management for this formidable disease that often presents with limited therapeutic options (Yew and Leung 2007). Nonetheless, data on cure rates tend to vary and are resource and setting-dependent. Mortality rate in a fifteen-year retrospective study of cases operated upon for pulmonary TB demonstrated 1.37% early and 2.83% late mortality. According to Dewan morbidity data reported in most other recent series, ranged from 3% to 53.7% (Dewan 2009). Kang and colleagues also presented their single institution data from surgical resections

performed on seventy-two patients with MDR or XDR TB. In their study, 93% of the MDR TB patients had favorable outcomes and 85% of XDR TB patients had a favorable outcome (Kang, Kim et al. 2010). Complications of surgical resections typically include respiratory failure, bronchopleural fistula, lung and other infections, empyema, wound bleeding and/or breakdown, as well as recurrent laryngeal nerve palsy (Yew and Leung 2007). Morbidity and mortality associated surgical management of the MDR or XDR TB patient show wide variance. This could be due to the fact that the definitions and criteria for assigning favorable outcome are researcher-dependent, as outcome-measures tend to be difficult to standardize. Patients with XDR TB tend to have very poor prognosis with high surgical treatment failure and mortality rates, and these were found to reach extremes in HIV co-infected patients. In the most alarming report from South Africa, mortality reached >90% among HIV infected patients (Yew and Leung 2007).

Treatment Outcomes for Drug-Resistant TB

The "Stop TB" strategy developed by WHO set the goal of curing 85% of all detected TB cases by 2005 (Orenstein, Basu et al. 2009). MDR TB has presented challenges to achieving the objective of the Stop TB Strategy in many areas. A recent systematic review and meta-analysis looked at the available therapeutic studies to characterize factors associated with improved treatment outcomes among patients with MDR-TB who were treated with second-line drugs. The analysis showed that the proportion of patients treated successfully improved when treatment duration was at least eighteen months, and if patients received directly observed therapy throughout treatment. Furthermore, it was observed that studies that combined both factors had significantly higher pooled success proportions (69%, 95%CI: 64–73%) than other studies of treatment outcomes (58%, 95% CI: 52–64%). Individualized treatment regimens had

higher treatment success (64%, 95% CI 59–68%) than standardized regimens (54%, 95% CI 43–68%), although the difference was not significant (Orenstein, Basu et al. 2009).

Another systematic review by Johnston and colleagues identified trials describing outcomes of patients treated for MDR TB. The review pooled appropriate data to estimate WHO-defined outcomes at the end of treatment and follow-up. In a pooled analysis, 62% (95% CI 57–67) of patients had successful outcomes, while 13% (9–17) defaulted, and 11% (9–13) died. Factors associated with worse outcome included male gender, alcohol abuse, smear positivity at diagnosis, fluoroquinolone resistance, and the presence of an XDR resistance pattern. Factors associated with successful outcome were surgical intervention, no previous treatment and fluoroquinolone use (Johnston, Shahidi et al. 2009).

Advances in Drug Development

Much progress has been made in drug development over the past decade (Lienhardt, Vernon et al. 2010). Yet, there remains the growing need for newer more active drugs that yield more successful treatment outcomes with fewer side effects. In addition to the discovery and development of new chemical entities, new chemotherapeutic advances may arise from optimizing the use of existing anti-TB drugs re-purposing existing antibiotics for use as anti-TB drugs (Nuermberger, Spigelman et al. 2010). Several new anti-TB agents are currently under clinical investigation. These include a number of potential drug candidates with new modes and mechanisms of action; these have recently entered clinical trials. They are likely to be effective against drug-resistant strains. Among them are a modified ethambutol, nitro-imidazole groups et cetera (Shi and Sugawara 2010). There is a global urgency to hasten their development and bring them to patients (Lalloo and Ambaram 2010).

Novel Technology in the Development of New Drugs

Researchers look to novel technologies as a means to find new compounds and as means to use available compounds to effectively treat TB. Like most drugs, many of the therapeutic agents available for managing the patient with TB have their limitations, such as instability, limited aqueous solubility, and bioavailability. Nanotechnology attempts to overcome some of the technological drawbacks of these therapeutic agents (Lalloo and Ambaram 2010). Since nanoparticles can be structured for sustained release from the medium, they also offer the ability to reduce dosing frequency. Liposomal formulations, like nanoparticles, have also been considered for similarly novel delivery systems of TB drugs. However, the promising flexibility with nanoparticles appears much greater than for liposome-encapsulated drugs. Capreomycin, a parenteral second-line drug, is being tested in human volunteers as an inhalational product. A respirable form of rifampicin (Rifampicin dihydrate, RFDH) was recently found to offer the benefit of delivering a maximum potency formulation of the antibiotic directly to the site of infection - the lung(Son and McConville 2011). Additional first-line drugs, and some investigational agents, have also been formulated and tested as inhalation therapy. Inhalational approaches are believed to deliver much higher doses of drug to the lung, although the exact histological localization of increased delivery is not clear (Nuermberger, Spigelman et al. 2010).Overall, the benefit of such new technology would be enhanced compliance and adherence, and subsequently better treatment outcomes (Lalloo and Ambaram 2010).

Vaccines

Over the past twenty years there has been a rapidly growing interest in developing new improved TB vaccines. The live attenuated Bacillus Calmette-Guérin (BCG) vaccine is still the only widely available vaccine against TB, despite the fact that it was developed more eighty

years ago. BCG is the most widely used vaccine available through the WHO Expanded Program for Immunizations (Svenson, Kallenius et al. 2010). Data on protective effect of the vaccine ranges from 0% to 77% , and the purported reasons for these variations are as variable as the data themselves (Svenson, Kallenius et al. 2010). Pending a clearer picture of the protective effect of the BCG vaccine, there is a growing need to come up with a new and effective vaccine that provided lasting protection.

In the search for new improved TB vaccines various approaches have been discussed, among which are genetically modified BCG, nucleic acid based vaccines, adjuvant killed whole-cell vaccines, subunits vaccines derived from recombinant protein antigens, carbohydrate-protein conjugates et cetera (Svenson, Kallenius et al. 2010). A recent study by Aagaard and colleagues showed that H56 vaccination after exposure is able to control reactivation and significantly lower the bacterial load in mouse models of latent TB (Aagaard, Hoang et al. 2011). While acknowledging the efforts to formulate a new boost vaccine that could provide lasting protection against TB, it is essential to remember that the greatest proportion of individuals targeted for any new TB vaccine live in low-income nations with poor medical infrastructures. Therefore, the cost to the consumer, the production and distribution or any such new vaccine should be within reason. The global community should jointly supply the needed budget, and the growing Private-Public-Partnership (PPP) movements and organizations like the Stop-TB Partnership hold great promise in this respect (Svenson, Kallenius et al. 2010).

Table 2: Desired properties of a novel TB vaccine, adapted from Svenson, Kallenius et al. 2010

Preferentially non-live i.e., killed or subunit type (increased stability, no cold chains needed, risk of reversion and liability problems are limited/ avoided)
If subunit, it should contain several targets from mycobacteria including essential proteins as well as carbohydrate antigens
It should be delivered in such a manner that it evokes relevant cellular (and humoral) immune responses systemically as well as via mucosa, in particular in respiratory tract
It should elicit a strong TH-1 response and, if needed, a non-toxic adjuvant should be used that supports such responses
It should be efficient not only as a primary vaccine but preferentially as a booster vaccine in the young adolescent after primary BCG vaccination

Conclusion and Recommendations

Over the past several years the number of global drug-resistant TB cases has been relatively stable, suggesting that further effort is needed to reduce the ongoing problem of drug-resistant TB. Although multiple factors drive the amplification and transmission of drug-resistant disease (e.g., immigration from endemic regions of the world, HIV co-infection, urban crowding, and suboptimal disease management and inadequate institutional infection control measures), one factor that can be addressed through training and education is the lack of expertise for complex issues in clinical care and management. Many drug-resistant cases result from either poor patient adherence to medication, suboptimal treatment regimens, or a combination of the two. By optimizing the treatment regimen, improving medical care and case management strategies, and

ensuring that patients take their medications using DOT, the likelihood of amplified drug resistance and transmission of drug-resistant TB will be decreased. Despite the headway made over the past several years in TB control, there is the need for further research in advanced therapeutics and prevention modalities. There is also the need for collaboration among the various stakeholders at the local and international levels.

This project has allowed for collaboration between the Centers for Disease Control and Prevention, Division of Tuberculosis Elimination, and the four Regional Training and Medical Consultation Centers (RTMCCs) in the United States, to create a product that will serve as a useful tool to increase provider knowledge about drug-resistant TB diagnosis and case management, as well as improve outcomes for individuals with drug-resistant TB. Ultimately, further work will be needed to evaluate the impact of this casebook on provider knowledge and its effect on patient outcome.

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