



Facing the Reality of Drug-Resistant Tuberculosis: Challenges and Potential Solutions in India: Summary of a Joint Workshop by the Institute of Medicine, the Indian National Science Academy, and the Indian Council of Medical Research

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Facing the Reality of Drug-Resistant Tuberculosis in India

Challenges and Potential Solutions

SUMMARY OF A JOINT WORKSHOP

by the Institute of Medicine,
the Indian National Science Academy, and
the Indian Council of Medical Research

Steve Olson, Rebecca A. English, Rita S. Guenther, and
Anne B. Claiborne, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation

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Willing is not enough; we must do.”*
—Goethe



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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for clarity, objectivity and responsiveness to the charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

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Acronyms

AIDS	acquired immune deficiency syndrome
AIIMS	All India Institute of Medical Sciences
API	active pharmaceutical ingredient
CAS	Central Asian
CDC	U.S. Centers for Disease Control and Prevention
CHW	community health worker
CPC	cetyl-pyridinium chloride
CRI	colorimetric redox indicator
DOT	directly observed treatment
DOTS	Directly Observed Treatment-Short course
DST	drug susceptibility testing
EAI	East African-Indian
EXPAND-TB	Expanding Access to New Diagnostics for TB
FIND	Foundation for Innovative New Diagnostics
GDF	Global Drug Facility
GLC	Green Light Committee
GLI	Global Laboratory Initiative
GMP	Good Manufacturing Practice
GP	general practitioner

HIV	human immunodeficiency virus
ICMR	Indian Council of Medical Research
INSA	Indian National Science Academy
IOM	Institute of Medicine
IRD	Interactive Research and Development
IRIS	immune reconstitution inflammatory syndrome
ISO	International Organisation for Standardization
IUATLD	International Union Against Tuberculosis and Lung Disease (“the Union”)
K-RITH	KwaZulu-Natal Research Institute for Tuberculosis and HIV
LAM	lipoarabinomannan
LED	light-emitting diode
LMIS	logistics management information systems
LPA	line probe assay
LRS	Lala Ram Sarup
MDR TB	multidrug-resistant tuberculosis
MGIT	mycobacteria growth indicator tube
MIRU	mycobacterial interspersed repetitive units
MODS	microscopic observation drug susceptibility
<i>M.tb.</i>	<i>Mycobacterium tuberculosis</i>
NAAT	nucleic acid amplification testing
NGO	nongovernmental organization
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NRA	nitrate reductase assay
PAS	P-aminosalicylic acid
PCR	polymerase chain reaction
PEPFAR	U.S. President’s Emergency Plan for AIDS Relief
PETTS	Preserving Effective TB Treatment Study
PKR	Pakistan rupees
PPM	public–private mix
RCC	Rolling Continuation Channel
RNTCP	Revised National Tuberculosis Control Program
SSCP	single-strand conformational polymorphism

TB	tuberculosis
TDR TB	totally drug-resistant tuberculosis
TLA	thin layer agar
TRC	Tuberculosis Research Centre (India) ¹
TST	tuberculin skin test
USAID	U.S. Agency for International Development
VNTR	variable number of tandem repeats
WHO	World Health Organization
XDR TB	extensively drug-resistant tuberculosis

¹ Since the workshop, the Tuberculosis Research Centre (TRC) in Chennai, India, was renamed the National Institute for Research in Tuberculosis.

1

Introduction¹

The workshop summarized in this volume was the third international meeting in a series sponsored by the Forum on Drug Discovery, Development, and Translation of the Institute of Medicine (IOM) to gather information from experts around the world on the threat of drug-resistant tuberculosis (TB) and how it can be addressed. The workshop was held April 18–19 and 21, 2011, in New Delhi, India, in collaboration with the Indian National Science Academy (INSA) and the Indian Council of Medical Research (ICMR).

The Forum held a foundational workshop in Washington, DC, in 2008. The summary of that workshop, *Addressing the Threat of Drug-Resistant Tuberculosis: A Realistic Assessment of the Challenge: Workshop Summary* (IOM, 2009), and the accompanying white paper (Keshavjee and Seung, 2008) provided background for and informed the development of four subsequent workshops in countries with a high burden of drug-resistant TB. The first international workshop in the series was held in Pretoria, South Africa, on March 3–4, 2010 (IOM, 2011a). The second international workshop was held in Moscow, Russia, on May 26–27, 2010 (IOM, 2011b). The final workshop in the series is being planned for China. Box 1-1 summarizes

¹ The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the Forum or the Institute of Medicine (IOM) and they should not be construed as reflecting any group consensus.

BOX 1-1^a**Key Viewpoints from Previous Workshops**

To set the stage for the workshop in India, Gail Cassell, Visiting Professor, Harvard Medical School, and Vice President of TB Drug Discovery, Infectious Disease Research Institute, provided an overview of selected key messages from the first three workshops held by the Forum in Washington, DC; Pretoria, South Africa; and Moscow, Russia (IOM, 2009, 2011a,b).

Global Surveillance of Drug-Resistant TB

According to Cassell, a clear message that emerged from these meetings is that the actual number of multidrug-resistant (MDR) TB cases is certain to exceed the 440,000 (range of 390,000 to 510,000) new cases estimated by the World Health Organization (WHO) to have occurred in 2008 (WHO, 2010b). Quality data on the incidence and prevalence of MDR TB are not always available for a country or region. Data from many countries are based on statistical modeling results rather than laboratory-based surveillance, often because the laboratories in countries with a high burden of MDR TB lack the capacity to test for susceptibility to second-line drugs.^b

Pediatric Drug-Resistant TB

Existing MDR TB surveys rarely include children. Cassell noted that even when children are included, they generally are lumped together into broad age groups, a practice that obscures the profile of pediatric MDR TB. If South Africa is an indication of the situation in other countries, Cassell said, MDR TB in children is a significant problem. According to a 2008 study of 148 children who underwent drug susceptibility testing (DST) while being treated for TB at two hospitals in Johannesburg, 8.8 percent, or 13 children, had MDR TB (Fairlie et al., 2011). Of those 13 children, 53.9 percent were HIV-coinfected, and 10 children received appropriate treatment. Four children with MDR TB died within 0.1 to 4.0 months after the date of TB investigation. In other studies presented at the Moscow meeting, data for Argentina and Peru indicated that MDR TB represented 15.4 percent of 136 previously treated TB cases in children in Argentina and 23.6 percent of 360 previously treated TB cases in children in Peru (IOM, 2011b; Llerena et al., 2010; Wright et al., 2009).

The microbiological diagnosis of drug-resistant TB in children is a challenge as children often have paucibacillary disease (few bacilli in sputum for testing), and specimens for DST are difficult to obtain. Cassell

suggested that to measure infection in the pediatric population accurately, the presence of the organism in other types of specimens must be detectable in a more sensitive way.

Transmission of MDR TB

Cassell noted that another strong message from the South Africa workshop was that human-to-human transmission of drug-resistant strains of TB is much more common than previously appreciated. In the past, infection control has been overlooked because there was a belief that drug-resistant strains are not spread as easily from person to person as susceptible strains. Whereas in the 1970s and 1980s, most MDR TB appeared to result from a lack of patient compliance with treatment or sequential treatment regimens, transmission of MDR and extensively drug-resistant (XDR) TB strains appears to dominate today, as evidenced by experience in Shanghai, South Africa, Tomsk, and Lima (IOM, 2011a,b).

Transmission of drug-resistant strains among children also is occurring in South Africa. In the 2008 South African study noted above, only 4 of the 13 children diagnosed with MDR TB had known exposure to an adult with TB, and none of these adult contacts had MDR TB (Fairlie et al., 2011). "Spread in the pediatric population is an important public health issue," said Cassell. Similarly, data presented at the Moscow workshop described 128 culture-confirmed pediatric cases in Colombia, South America. Almost all of these cases had never been treated, and most had no history of adult MDR TB contacts.

Diagnosis and Treatment of MDR TB

As discussed in a white paper prepared for the Washington, DC, workshop (Keshavjee and Seung, 2008), the number of patients receiving treatment for TB worldwide is small, and in many cases the treatment they are receiving is ineffective because it is not based on DST. Rather, patients have failed treatment with first-line drugs and therefore have been put on second-line drugs without the susceptibility of their TB strain to those drugs being known. In 2010, only 16 percent of global MDR TB cases estimated to exist among reported TB cases were actually enrolled in MDR TB treatment regimens (WHO, 2011a). It is also estimated that as of 2010, fewer than 5 percent of TB patients were being tested for MDR TB in most parts of the world (WHO, 2011a).

Cassell cited the views expressed by some speakers at previous workshops that while enhancing laboratory capacity might improve surveillance, it would be unlikely to affect individual patient treatment and thus would fail to affect the spread of drug-resistant strains. It is

continued

BOX 1-1 Continued

unrealistic to think that in countries that currently have fewer than 1 laboratory per 10 million population, which is the case in most high-burden countries, sufficient resources and time would be available to scale up capacity quickly enough to have a major impact on rapid diagnosis and treatment, especially given that most patients are in remote settings. Countries need one laboratory per 5 million population to perform culture and DST, according to standards developed by WHO (2011a). Of 27 countries with a high burden of MDR TB, however, just 13 meet both of these standards (Armenia, Azerbaijan, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, South Africa, and Ukraine).

Recently introduced diagnostics and technologies in late-stage development increase the speed and sensitivity of diagnosis. GeneXpert, for example, is an impressive advance. But a diagnostic still is needed that can determine antimicrobial susceptibility quickly at the point of care so that patients can be managed appropriately. Also, new technologies still require laboratory infrastructure and have limited capability to detect MDR genes or to detect infection other than in sputum.

The three previous workshops also emphasized the importance of the procurement and distribution of high-quality drugs. Critical issues include the need for better data on drug quality, quality enforcement, quality strategies, and accurate demand forecasting.

One of the most urgent needs is to obtain accurate data on the existence of totally drug-resistant (TDR) TB, said Cassell, because only then will the rest of the world take notice of the problem and policy makers increase funding for its control. Striking new data from KwaZulu-Natal reveal the magnitude of the problem: in the studied population, 88 percent of cases identified as XDR TB were actually TDR.^c Even under the best of circumstances—as has been the case in Tomsk (Keshavjee et al., 2008) and in Peru (Mitnick et al., 2008)—only 48 percent and 60 percent, respectively, of XDR TB cases are treatable, which means that 52 and 40 percent, respectively, are untreatable. Currently there are no consistent policies for dealing with patients whose TB is untreatable. Proof that the disease in these patients is untreatable may take months, during which time they may spread their resistant organisms to family members and others in the community, including health care workers.

Development of New Antibiotics

Successfully treating these patients will require not just one new antibiotic in the regimen but a combination of three to four new classes of antibiotics simultaneously. This represents an enormous financial and technical challenge requiring massive cooperation. Today the failure rate from the time of target identification to regulatory approval of a new drug is 90 percent. Half of drugs fail even in phase III clinical trials. The average cost of developing a new drug is more than \$1.5 billion, and the average time for drug discovery and development from target identification to approval is 10 to 14 years. Both of these figures would probably be higher for TB drugs given the lack of infrastructure and point-of-care diagnostics in high-burden countries. Yet in 2010, the world was investing only \$226.8 million in TB drug research and development from all sources (Treatment Action Group, 2011).

According to Cassell, the public perception is that TB remains a problem but that drugs are available to treat it. The reality is that MDR and XDR TB are increasing at a rapid rate. As noted, current estimates are that 440,000 new cases of MDR TB are occurring each year, which is not a large number compared with other unmet medical needs. However, the reality is that while the number of patients diagnosed with and treated for MDR TB is increasing globally, the majority of MDR TB patients are not diagnosed and not receiving treatment. Only 16 percent of the TB patients estimated to have MDR TB in 2010 were diagnosed and given appropriate treatment (WHO, 2011a,b; Zignol et al., 2012).

^a This box is based on the presentation of Gail Cassell, Visiting Professor, Harvard Medical School, and Vice President of TB Drug Discovery, Infectious Disease Research Institute.

^b A report from WHO (2011a) released after the workshop indicates that 60 percent of countries currently have at least one direct and representative measurement of drug resistance among their TB patients. Despite overall global increases in the coverage of data on drug resistance, however, considerable uncertainty remains as to the actual levels of MDR TB among TB patients.

^c Data provided via personal communication, June 22, 2011, with Kristina Wallengren, Acting Clinical Core Manager, KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH), Nelson R. Mandela School of Medicine, University of KwaZulu-Natal.

key viewpoints and findings from the workshops held previously in Washington, Pretoria, and Moscow.

The workshop in India brought together about 100 disease experts, community leaders, policy makers, and patient advocates from India, the United States, and other countries for 2 days of intensive discussions. While the workshop was specifically designed to address the current status of drug-resistant TB in India, the presentations and discussions were anchored in a framework reflective of the global experience with MDR TB. The aim of the workshop was to highlight key challenges to controlling the spread of drug-resistant strains of TB and to discuss innovative strategies for advancing and harmonizing local and international efforts to prevent and treat drug-resistant TB.²

HISTORY AND DIMENSIONS OF THE PROBLEM³

Evidence indicates that TB has plagued mankind since ancient times, said Prakash N. Tandon, Emeritus Professor, INSA, in his opening remarks at the workshop. A human skeleton from a Neolithic cemetery near Heidelberg, Germany, dating to 5000 BCE shows evidence of spinal TB. Of interest, said Tandon, is evidence in this skeleton of healing in the absence of any drugs. Egyptian skeletons dating back to 3500 BCE likewise show evidence of TB. Hymns in the Rigveda and Yajurveda indicate that the early Indo-Aryans were familiar with the disease in the second millennium BCE.

Today, an estimated 2 billion people, one-third of the global population, are infected with *Mycobacterium tuberculosis* (*M.tb.*), the bacterium that causes TB (Keshavjee and Seung, 2008). Spread through the air, this infectious disease killed 1.7 million people in 2009, or approximately 4,700 people each day (WHO, 2010a).

Although antibiotics developed in the 1950s are effective against a large

² The National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health (NIH), held a meeting focused on exploring opportunities for collaboration in TB drug discovery research on April 20–21, 2011, the 2 days following the IOM workshop, also in New Delhi. The NIAID meeting was cosponsored by the Department of Biotechnology, Ministry of Science and Technology, Government of India, and ICMR. Meeting objectives included sharing the latest scientific information on drug discovery research focused on combating MDR and XDR TB, discussing TB drug development needs and the ways in which biomedical research can contribute, and identifying partnership opportunities to advance and accelerate new drug discovery efforts in order to simplify and improve therapeutic options for drug-resistant TB. Topics and meeting participants overlapped between the NIAID and IOM meetings in India, creating synergies and connections for future collaborations in the areas of TB research and policy. Appendix B of this report includes a summary of the NIAID meeting.

³ This section and the two that follow are based on the welcoming remarks of Prakash N. Tandon, Emeritus Professor, INSA; Krishan Lal, President, INSA; and Vishwa Mohan Katoch, Director General, ICMR.

percentage of TB cases, resistance to these first-line therapies has developed over the years, resulting in the growing emergence of MDR and XDR TB (see Box 1-2 for definitions). Diagnosing and effectively treating MDR and XDR TB patients requires increasingly complex public health interventions. MDR TB, for example, is resistant to first-line drugs and must be treated with second-line drugs that are more expensive and more toxic, often require injection, and involve longer treatment regimens (2 years or more to treat MDR TB compared with 6–9 months to treat drug-susceptible TB). As drug resistance develops, the challenge is to stop the transmission or spread of MDR TB and identify MDR TB cases early; treatment should include efforts to preserve the effectiveness of current drugs and create new treatment regimens to combat drug-resistant strains as they emerge.

THE BURDEN OF DRUG-RESISTANT TB

According to data from WHO on global drug resistance, an estimated 3.6 percent of global incident (new) TB cases, or a total of 440,000 cases, were MDR TB in 2008 (95 percent confidence interval, 390,000-510,000) (WHO, 2010c).⁴ The available data on drug-resistant TB are inadequate, however, and lead to an underestimation of the true global burden of MDR TB. In many developing countries where the MDR TB burden is likely to be significant, surveillance systems do not exist or lack the capacity to generate reliable data. Even the most recent global surveillance data on MDR TB do not include 79 countries—41 percent of all countries in the world (WHO, 2010c, p. 6).

The burden of XDR TB is even less well known because many countries lack the laboratory and infrastructure capacity necessary to test MDR TB patients routinely for susceptibility of their infection to second-line drugs. The provision of optimal patient care for MDR and XDR TB patients is based on DST, and many countries are ill equipped to conduct such tests. It is through such testing that physicians determine which drugs are likely to be effective against a particular drug resistance profile. The vast majority of MDR and XDR TB cases are undetected and thus untreated with appropriate second-line drugs. Of those patients who are treated with second-line drugs, many are not taking the right drugs to treat their drug resistance profile effectively.

⁴ Instead of providing a global estimate of incident MDR TB cases each year, an updated WHO (2011a) report on TB control, released after the workshop, estimates the prevalence of MDR TB (number of cases) globally. According to that report, an estimated 650,000 MDR TB cases existed among the world's 12 million cases of TB in 2010. (*Prevalence* measures the level of a disease in a population at a particular point in time, while *incidence* measures the occurrence of new cases of a disease in a population.)

BOX 1-2^a The Nature of the Threat

Definitions

Multidrug-resistant (MDR) TB is caused by bacteria resistant to isoniazid and rifampicin, the two most effective first-line anti-TB drugs, originally developed and introduced in the 1950s and 1960s.

Extensively drug-resistant (XDR) TB is resistant to the same drugs as MDR TB (isoniazid and rifampicin), as well as any fluoroquinolone (levofloxacin, moxifloxacin, or ofloxacin) and at least one second-line injectable drug (kanamycin, amikacin, or capreomycin).

Totally drug-resistant (TDR) TB is TB for which no effective treatments are available.

Pathways for Infection

MDR/XDR TB results from either **primary infection** with a drug-resistant strain of TB (i.e., transmitted by person-to-person contact) or **acquired infection** with such a strain that occurs in the course of a patient's treatment, resulting, for example, from failure to ensure regular treatment with high-quality existing drugs. **Amplified resistance**, or the enhancement of existing drug resistance as a result of initiating an inappropriate drug regimen at the beginning of care, is a significant challenge

TREATING TB IN CONTEXT

The diagnosis of TB is no longer a death warrant, said Krishan Lal, President, INSA, but the existence of treatments raises sociological and psychological issues. Patients may take a treatment just until they feel well, which can foster the development of resistance and lead to the spread of the disease. In addition, many health problems other than TB, such as diabetes and high blood pressure, occur in India, which can complicate treatment. The lack of quick, accurate, and inexpensive tests for drug-resistant TB hampers treatment, said Tandon. Drug-resistant TB needs to be diagnosed earlier and with greater specificity than is currently the case, especially given the much greater costs of treating drug-resistant TB.

created by providing an incorrect combination of drugs. For example, a patient might display resistance to streptomycin and isoniazid at the beginning of treatment and subsequently become resistant to streptomycin, isoniazid, and rifampicin during the course of treatment. Even when an empirically appropriate drug regimen is selected at the beginning of treatment, by the time drug susceptibility information is available, resistance may be amplified.

WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) have urged replacement of the term “primary resistance” with “drug resistance among new cases” and the term “acquired resistance” with “drug resistance among previously treated cases.”

Treatment

MDR/XDR TB treatment requires 2 years or more of daily, directly observed treatment (DOT) with drugs that are less potent, more toxic, and much more expensive than those used to treat drug-susceptible TB. Despite the challenges, aggressive treatment with second-line drugs has produced positive outcomes in MDR/XDR TB patients. However, TDR TB is a growing threat. The spread of TDR TB is especially ominous as it would return the globe to the pre-antibiotic era (Keshavjee and Seung, 2008).

^a The information in this box was originally presented at the Forum’s 2008 workshop on drug-resistant TB (IOM, 2009).

India has in the past had great success in tackling major health problems such as leprosy, observed Vishwa Mohan Katoch, Director General, ICMR. The country has instituted a massive program to deliver drugs to TB patients, but the disease also needs to be monitored and managed very carefully. Comprehensive approaches, such as those reflected in the agenda of this workshop, are essential, V. M. Katoch said.

Tandon, Lal, and V. M. Katoch praised the extent of international collaboration in responding to drug-resistant TB, especially the collaboration between India and the United States. Both countries are members of the Global Network of Academies, Lal observed, and this organization also has worked with the InterAcademy Medical Panel. Such collaborations will be essential, he said, for evolving strategies to fight TB.

OVERVIEW OF TB AND MDR TB IN INDIA⁵

In his opening keynote address, K. Srinath Reddy, President, Public Health Foundation of India, provided a broad overview of TB in India and the nation's response to the disease. (Chapter 2 covers these topics in greater detail.)

India accounts for approximately one-fifth of the global incidence of TB (RNTCP Status Report, 2011). Fully 40 percent of the country's population is infected with the tubercule bacillus. Each year the country sees 2 million new cases (the global incidence is 9.4 million), which lead to 280,000 deaths annually, although the prevalence of HIV among new cases in India is just 6.4 percent compared with a global average of 12 percent. TB is one of the leading causes of death among adults in India, and it also takes a large toll on the country's younger generation, which makes up a significant proportion of the total population.⁶ TB also takes a disproportionately large toll among young females: more than 50 percent of TB cases among females occur before age 34, and an estimated 100,000 women are rejected by their families every year because they have the disease. Some workshop participants noted that national-level, all-India studies evaluating the effect of a TB diagnosis on family dynamics could provide more specific data and have an impact on understanding and preventing the rejection of TB patients by their families.

TB also disproportionately affects the poorest and most marginalized populations in India, as well as people in their most productive ages—70 percent of TB patients are aged 15–54. People with TB incur an average potential loss of 20–30 percent of their annual household income as a result of 3–4 months of lost work time. In India, about 14 million people fall into poverty each year because they experience unaffordable health care costs, and TB is a major cause of health-related impoverishment.

Drug-Resistant TB in India

Reddy noted that, based on 2008 data, MDR TB represents an estimated 2.3 percent of new TB cases in India (compared with 3.3 percent

⁵ This section is based on the presentation of K. Srinath Reddy, President, Public Health Foundation of India.

⁶ According to the 2001 Indian census, the country has a large proportion of young people—35 percent of the population is aged 14 and younger (Government of India, 2001). Provisional population totals from the 2011 Indian census reveal a total population of 1.21 billion people, reflecting an additional 181 million people since 2001. The United Nations has estimated that the world population grew at an annual rate of 1.23 percent from 2000 to 2010. Over this decade, China's population grew at an annual rate of 0.53 percent and India's at an annual rate of 1.64 percent (Government of India, 2011).

worldwide) and 17 percent of retreatment cases. These figures represent about 99,000 MDR TB cases in the country.

XDR TB has been reported in India. However, its magnitude remains undetermined because of a lack of laboratories capable of conducting quality-assured second-line DST.⁷

The Revised National TB Control Program

The United Nations' Millennium Development Goals call for halting and beginning to reverse the incidence of TB by 2015. The STOP TB Partnership has established the target of reducing the global burden of TB (defined by per capita prevalence and death rates) by 50 percent relative to 1990 levels by 2015 and the long-term goal of reducing the global incidence of active TB to less than 1 case per million population per year by 2050.

India's strategy for working toward these goals is embodied in its Revised National TB Control Program (RNTCP). This program is structured around five elements:

1. political and administrative commitment;
2. good-quality diagnosis, primarily by sputum smear microscopy;
3. an uninterrupted supply of quality drugs;
4. DOT; and
5. systematic monitoring and accountability.

A massive expansion of the program began in 1998, so that by 2006, Directly Observed Treatment-Short course (DOTS) coverage had been extended to 632 districts and more than 1.1 billion people.

In 2010, DOTS-Plus services were introduced in some states of India to treat MDR TB. By 2012, these services will have been extended to all smear-positive retreatment cases and to new cases that have failed an initial first-line drug treatment. By 2015, services are to be made available to all smear-positive pulmonary TB cases registered under the program. By 2012–2013, the program's goal is to treat at least 30,000 MDR TB cases annually. Providing DOTS-Plus for MDR TB requires giving special attention to several key factors in program design and delivery:

⁷ The emergence of what has been described as TDR TB was reported in January 2012 (Udwadia et al., 2012) at Hinduja Hospital in Mumbai when four patients were found to be resistant to all first- and second-line drugs tested. India's Revised National TB Control Program (RNTCP) has issued a response to the report and provided information on the program's approach to combating all forms of drug-resistant TB. For more information, visit <http://tbcindia.nic.in/pdfs/RNTCP%20Response%20DR%20TB%20in%20India%20-%20Jan%202012%20update.pdf> (accessed April 17, 2012).

- quality-assured laboratory capacity for smear, culture, and drug sensitivity testing;
- treatment design;
- adherence to difficult-to-take regimens for long periods of time;
- management of side effects;
- drug procurement;
- recording and reporting; and
- human and financial resource constraints.

As of the end of 2010, MDR TB treatment had been scaled up to cover 287 million people in 139 districts across 12 states of India. Since the inception of services, more than 19,000 suspected MDR TB cases have been examined for diagnosis, more than 5,000 cases have been confirmed, and more than 3,500 cases have been initiated on category IV treatment through 20 DOTS-Plus sites.

Reddy noted that in general, India has a strong national program for basic TB control with a high treatment success rate. The country has made provisions for the participation of all health care providers, including private practitioners. Efforts also have been made to control the dual epidemics of TB and HIV (see the discussion of this topic in Chapter 6). Extensive laboratory expansion is planned in collaboration with the private sector, which has to date been a largely untapped resource in the development of laboratory capacity. (The expansion plans for the program are described in Chapter 2 and public–private participation in Chapter 7.)

Challenges in the Management of MDR TB in India

Several challenges are faced in the management of MDR TB in India, said Reddy. First is the limited supply of human resources to carry out training and assessments. Indeed, India is a country where in general, human resources in health care are limited and not well distributed. According to Reddy, the country's public health workforce needs to be expanded, and those who are currently employed need training to augment their knowledge and skills.

Second, there is a lack of funding for the management of MDR TB, especially given the high cost of second-line drugs as treatment is scaled up. A high-level expert group recently recommended that a larger portion of the country's health budget be allocated to providing drugs free of cost and that the national capacity to produce and supply low-cost drugs, including public procurement, be enhanced (Planning Commission of India, 2011). Other workshop participants noted that policy implementation delays will negatively affect MDR TB cases—diagnosed and undiagnosed.

Third, laboratory capacity for diagnosis and follow-up of MDR TB

patients and quality assurance is limited. Although expansion currently is taking place, India now has only 23 functional laboratories across the country, and according to Reddy, many more are needed. The availability of second-line drugs and DST also is limited. High-throughput diagnostics and a specimen transportation infrastructure are particular needs. An MDR TB surveillance or survey program still does not exist, and an infection control plan is lacking. Reddy stressed that all of these issues need to be addressed and that managerial capacity must be improved as well. India needs a strong vertical program that integrates all aspects of MDR TB control and care, including infection control, diagnosis, treatment, and follow-up. However, Reddy added, it is difficult to impose a strong vertical program on a weak national health system.

The Need for Action

The prevalence of MDR and XDR TB in India and globally raises the possibility that the current epidemic of mainly drug-susceptible TB will be replaced by a form of TB with severely restricted treatment options, Reddy observed. If so, plans to move toward a world where TB is no longer a public health problem will be derailed.

Reddy stressed that the basic TB program in India needs to be strengthened to reach out to unnotified and missed cases and to poor and highly vulnerable populations. More broadly, the social determinants of TB need to be addressed. The Public Health Foundation of India is currently working with the RNTCP to assess the barriers experienced by vulnerable groups in accessing services and determine how those barriers can be overcome.

In terms of surveillance, India's Department of Health Research needs to supplement efforts currently in place, particularly for MDR and XDR TB, said Reddy. Laboratory networks need to be strengthened and expanded, human resources and financial management need to be enhanced, and the drug supply chain needs to be strengthened. Reddy also noted that the National Board of Examinations is currently connected to more than 700 hospitals that are distributed across the country and have postgraduate trainees who are expected to conduct research. According to Reddy, "If at least 100 of these hospitals can be linked up and their surveillance changed to regularly report on issues related to MDR TB and XDR TB—in terms of detection as well as management and outcomes—we can develop a centralized surveillance system across the country extending to medical colleges." In this way, India could quickly build a cost-effective surveillance system that would be nationally representative.

Policies should ensure that all TB patients have equitable access to care and that their interests and rights are protected, said Reddy. Policies also should ensure that all relevant public and private health care providers are

engaged in managing TB according to national priorities. And the primary health care system should be strengthened to ensure early detection, effective treatment, and support for patients.

Reddy emphasized that TB medicines should be sold by prescription only and should be prescribed and dispensed by accredited public and private providers. He noted that in India today, drugs often are sold over the counter instead of through appropriate prescriptions, a situation that can foster misuse. Infection control policies are needed, and investments should be made to promote research, surveillance, molecular diagnostics, and drug development.

Reddy concluded by lauding the collective commitment to combating drug-resistant TB, “which now transcends geographical barriers and also brings scientific coalescence from multiple disciplines.” In this context, he suggested, “this workshop should be a landmark for initiating action against MDR TB and XDR TB.”

SETTING THE STAGE⁸

To set the stage for the remainder of the workshop, Salmaan Keshavjee, Assistant Professor, Harvard Medical School, provided a global overview of the challenges and potential solutions in confronting drug-resistant TB (discussed in detail in Chapter 3), with an emphasis on the slow pace of treatment scale-up and the consequences of inaction. He urged the participants “to be blunt with each other, because we are TB experts, and if we can’t be honest with each other, we are going to have big trouble as we move forward.” To this end, throughout the workshop, there was discussion of existing bottlenecks and challenges, as well as examples of incentives and disincentives from other locations or experiences. Experiences with both success and failure were shared.

In 2006, the STOP TB Partnership established a plan for combating the epidemic of drug-resistant TB. At that time, WHO was estimating that about 500,000 new cases of drug-resistant TB occurred each year, meaning that between 2006 and 2015 there would be 5 million cases. The goal of the 2006 plan was to treat 1.6 million cases, said Keshavjee, leaving the other 3.4 million without treatment; he referred to this target as “dismal.”

Since that plan was established, official efforts to treat MDR TB have failed to achieve even this target, Keshavjee stated. Of the 5 million cases estimated to have occurred between 2000 and 2009, only approximately 22,000 patients received treatment through programs approved by the Green Light Committee (GLC)—a multilateral coal-

⁸ This section is based on the presentation of Salmaan Keshavjee, Assistant Professor, Harvard Medical School.

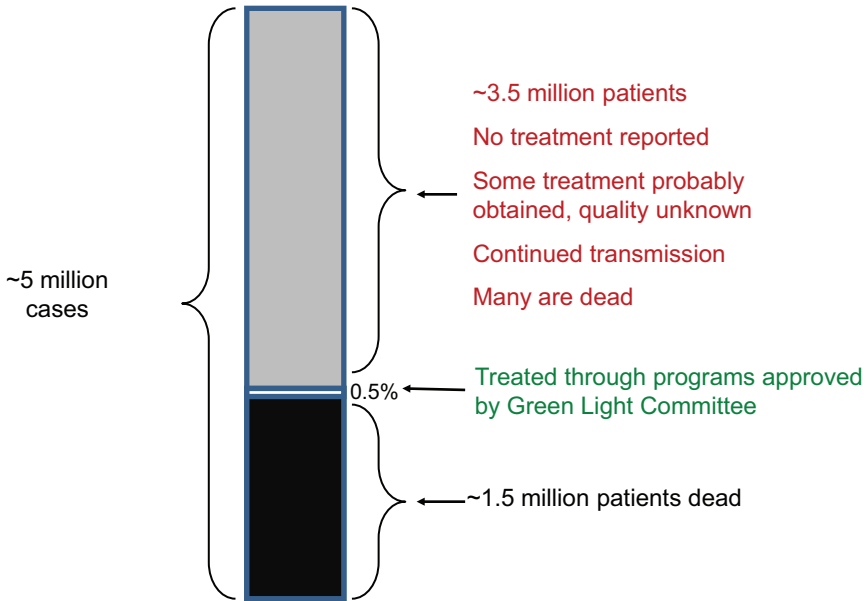


FIGURE 1-1 Of the estimated 5 million MDR TB cases that occurred between 2000 and 2009, only 0.5 percent were treated in programs approved by the Green Light Committee.

SOURCE: Keshavjee, 2011a.

tion created in 2000 (Figure 1-1). About 3.5 million of the 5 million patients received no reported treatment, although an unknown fraction undoubtedly received some treatment of unknown quality from private physicians, pharmacies, or other sources. Meanwhile, many continued to transmit the disease while alive. According to global statistics, 1.5 million of these 5 million people died. Keshavjee emphasized that this is an epidemic of profound proportions.

Scaling up treatment for drug-resistant TB is complex, Keshavjee acknowledged. But treating HIV in poor countries is also complex, and the global community has done a much better job of that. Between 2004 and 2008, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) provided antiretroviral therapy to more than 1.6 million people, including 367,000 patients who were coinfecting with HIV and TB. The contrast between the responses to TB and HIV, said Keshavjee, calls for a rethinking of the global approach to TB.

ORGANIZATION OF THE REPORT

This report summarizes the main points made at the workshop in India during both the formal presentations and the discussions among participants. In accordance with IOM and National Research Council policies, this report provides an accurate summary of the presentations and discussions held at the workshop; it does not contain any commentaries or views that were not presented at the workshop, and any supplementary viewpoints shared outside of the workshop context are not included in this summary. Observations and recommendations made by individual speakers and participants do not represent the formal positions of the planning committee, the Forum, the IOM, INSA, or ICMR; however, they have provided valuable input to the Forum and to the IOM and the workshop contributors as they deliberate on future initiatives. Presentations at the workshop addressed the following topics:

- TB and MDR TB in India, including local and national responses to the epidemic (Chapter 2);
- the global burden of TB and drug-resistant TB, including data from another high-burden country, China (Chapter 3);
- prevention of the transmission of drug-resistant TB in India (Chapter 4);
- rapid methods of detecting drug resistance and strengthening laboratory capacity (Chapter 5);
- approaches to reaching vulnerable populations affected by drug-resistant TB (Chapter 6);
- public-private engagement and innovative methods in combating drug-resistant TB (Chapter 7);
- the drug supply chain for second-line drugs (Chapter 8); and
- the major viewpoints expressed at the workshop and next steps suggested by workshop participants (Chapter 9).

Each of these chapters opens with a box listing the key messages emerging from the workshop presentations and discussions, as identified by the workshop rapporteurs.

2

Drug-Resistant TB in India¹

Key Messages

- India accounted for 24 percent of the 5.7 million new and relapse TB cases notified globally in 2010 (WHO, 2011a).
- India had the second highest total number of estimated MDR TB cases (99,000) in 2008, after China (100,000 cases) (WHO, 2010b).
- Drug resistance surveys in several states have indicated that the prevalence of MDR TB in India is 2–3 percent among new cases and 12-17 percent among reinfection cases.
- India's RNTCP has an overall goal of providing universal access to quality diagnosis and treatment for all TB patients, with an intermediate goal of successfully treating at least 90 percent of all new and at least 85 percent of all previously treated patients.

continued

¹ This chapter is based on the presentations of Ashok Kumar, Deputy Director General and Head, Central TB Division, and Project Director, RNTCP; Kuldeep Singh Sachdeva, Chief Medical Officer, Central TB Division; S. K. Sharma, Chair, Department of Medicine, All India Institute of Medical Sciences (AIIMS); Rohit Sarin, Senior Consultant, Lala Ram Sarup (LRS) Institute of Tuberculosis and Respiratory Diseases; and Aleyamma Thomas, Scientist G and Director-in-Charge, National Institute for Research in Tuberculosis. (Since the workshop, the Tuberculosis Research Centre [TRC] has been renamed the National Institute for Research in Tuberculosis. For the remainder of this workshop summary report, the organization will be referred to by its current name.)

Key Messages Continued

- The RNTCP is scaling up the number of culture and DST laboratories nationwide, along with treatment services, including DOTS-Plus.
- Despite these achievements, India's efforts to control TB and MDR TB still suffer from too few laboratories, slow diagnostic tools, inadequate management of treatment, insufficient supplies of second-line drugs, and shortages of trained personnel.
- Community-based MDR TB treatment is being implemented as an alternative model of treatment.
- Data from the RNTCP from 2007 to 2010 indicate that the majority of MDR TB cases were undiagnosed in India.

Drug-resistant TB has existed in India virtually since anti-TB drugs were introduced into the country. ICMR carried out state-of-the-art surveys for drug-resistant TB more than 40 years ago (ICMR, 1968, 1969), and surveys have continued since then (Paramasivan and Venkataraman, 2004). Resistance to rifampicin, streptomycin, and other anti-TB drugs has been detected for decades, and MDR TB also was seen in early surveys, although at different levels depending on the place, time, and testing parameters. However, the increasing burden of drug-resistant TB introduces new challenges to TB control and treatment. Ashok Kumar, Deputy Director General and Head, Central TB Division, and Project Director, RNTCP; Kuldeep Singh Sachdeva, Chief Medical Officer, Central TB Division; S. K. Sharma, Chair, Department of Medicine, All India Institute of Medical Sciences (AIIMS); Rohit Sarin, Senior Consultant, Lala Ram Sarup (LRS) Institute of Tuberculosis and Respiratory Diseases; and Aleyamma Thomas, Scientist G and Director-in-Charge, National Institute for Research in Tuberculosis, described the current status of TB and MDR TB in India and the actions taken by government at various levels to combat the disease.

THE BURDEN OF TB AND MDR TB IN INDIA²

India has the highest TB burden of any country in the world, accounting for an estimated one-fifth of global TB cases worldwide (Figure 2-1). It has an estimated prevalence of 3 million TB cases, with 2 million new cases

² This section is based on the presentation of Kuldeep Singh Sachdeva, Chief Medical Officer, Central TB Division.

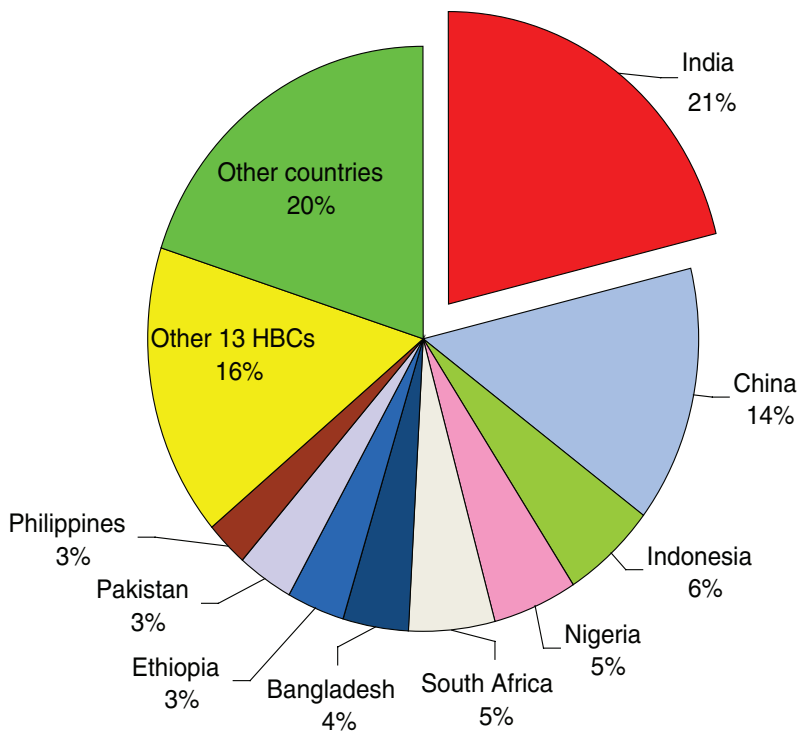


FIGURE 2-1 India has the highest TB burden of any country in the world. As of the date of the workshop, annual incidence was 2 million cases, estimated prevalence was 3 million, annual deaths due to TB totaled 280,000, and approximately 6.4 percent of incident TB cases were also HIV-positive.

NOTE: HBC, high-burden country.
 SOURCE: Sachdeva, 2011. Based on data from Global Tuberculosis Control: WHO Report 2010 (WHO, 2010b).

occurring each year. About 280,000 people die from TB in India annually.³ India has the second highest burden of MDR TB in the world after China, with an estimated 99,000 new cases per year (WHO, 2010b).

Sachdeva noted that the RNTCP carried out a drug resistance surveillance survey in accordance with global guidelines in the states of Gujarat and Maharashtra in 2007 and in Andhra Pradesh in 2009 (Table 2-1). The results of these selected surveys indicate an MDR TB prevalence of about

³ Since the workshop took place, an updated WHO report (2011a) cited new provisional estimates of the TB burden in India in 2010. India has an estimated prevalence of 3.1 million TB cases, with 2.3 million new cases occurring each year, and 320,000 deaths due to TB each year.

TABLE 2-1 Drug Resistance Surveillance in Three Indian States

State (survey year)	Population	MDR TB Among New Cases (%)	MDR TB Among Previously Treated Cases (%)
Gujarat (2007–2008)	56 million	2.4	17.4
Maharashtra (2008)	108 million	2.7	14.0
Andhra Pradesh (2009)	86 million	1.8	11.8

SOURCE: Sachdeva, 2011.

2–3 percent among new cases and 12–17 percent among previously treated cases.

According to Sharma and colleagues (2011a), the prevalence of MDR TB among 177 cases of newly diagnosed pulmonary TB patients in New Delhi in 2008–2009 was lower—about 1.1 percent. Among 196 patients with pulmonary TB diagnosed in New Delhi between 2005 and 2008 who had failed previous TB treatment, relapsed after treatment, or defaulted during treatment, 20.4 percent had MDR TB (Sharma et al., 2011b).

Population-based data are highly limited for second-line drug resistance among MDR TB patients, according to Sachdeva. According to drug resistance surveillance data from Gujarat, fluoroquinolone resistance occurred in 24 percent and kanamycin resistance in 3 percent of 219 MDR TB cases detected. XDR TB was observed in about 3 percent of MDR TB isolates, and all 7 of these cases were in previously treated patients.

Accurate estimates of drug resistance require that results come from well-qualified and accredited laboratories. The reliability of the data and quality control issues are essential considerations both in estimating current levels and in making historical comparisons, noted Sharma.

PLANS OF THE REVISED NATIONAL TB CONTROL PROGRAM⁴

Initiated in 1997, the RNTCP has been implementing all of the components of the WHO STOP TB Partnership, including early diagnosis, quality smear microscopy, and prompt treatment with DOTS using quality first-line drugs, said A. Kumar. Sachdeva noted that the RNTCP's overriding goal is to provide universal access to quality diagnosis and treatment for all patients. Intermediate goals (by 2015) are to achieve early detection of at least 90 percent of all TB cases, including HIV-associated TB; perform initial screening of all smear-positive patients for drug-resistant TB; provide

⁴ This section is based on the presentations of Kuldeep Singh Sachdeva, Chief Medical Officer, Central TB Division; and Ashok Kumar, Deputy Director General and Head, Central TB Division, and Project Director, RNTCP.

HIV counseling and testing for all TB patients; and successfully treat at least 90 percent of all new and at least 85 percent of all previously treated TB patients. A national strategy for the RNTCP for the next Five-Year Plan, which extends from 2012 to 2017, is currently being developed. Since the RNTCP's inception, more than 12 million TB patients have been initiated on DOTS, and approximately 2 million lives have been saved, A. Kumar noted.

Preventing Drug-Resistant TB

To combat drug-resistant TB, the RNTCP has developed a multiphase response plan, said A. Kumar. With regard to prevention, the plan calls for improving and sustaining high-quality DOTS implementation, promoting the rational use of anti-TB drugs, and implementing infection control measures. The RNTCP is also seeking to improve laboratory capacity, effectively treat MDR TB patients, initiate and rapidly scale up MDR TB services, and evaluate the extent of second-line anti-TB management strategies.

Airborne infection control is crucial for preventing the spread of TB from person to person, as well as reducing the risk of TB among health workers in institutional settings, said A. Kumar. The National Airborne Infection Control Committee was established in 2008 with representatives from the medical profession, the National Center for Disease Control, the National Center for TB Resistance, WHO, architects, and engineers. The committee has developed provisional guidelines on airborne infection control in health care and other settings. These guidelines are expected to augment the infection control measures undertaken by the RNTCP. Workshops on airborne infection control have been organized by the RNTCP with the support of the U.S. Centers for Disease Control and Prevention (CDC), WHO, and others, and pilot implementation programs have been initiated. The RNTCP also has disseminated provisional airborne infection control guidelines to all states in India.

A. Kumar noted that the national guidelines for infection control still need to be operationalized, not just for TB but for the general health system and at the community level. Chapter 4 of this report summarizes several workshop presentations specifically addressing infection control.

Diagnosing Drug-Resistant TB

Sachdeva reported that a staggered approach is currently being used to diagnose MDR TB in India. MDR TB is suspected in all patients who fail the first-line drug regimen, all patients whose sputum is positive after 4 months of treatment, and all smear-positive contacts of MDR TB patients. These

criteria will be changed over the years as laboratory capacity expands. DST is conducted at an accredited laboratory, with the line probe assay (LPA) being the preferred testing method if available. Treatment is initiated on the basis of results for rifampicin resistance, since resistance only to rifampicin is rare.

Edward Nardell, Associate Professor of Medicine, Harvard Medical School, pointed out that because previously untreated TB cases are much more numerous than those previously treated,⁵ more than half of MDR TB cases globally are new. However, more effort is required to detect such cases.⁶ A strategy that focuses on smear-positive patients for MDR TB testing will be more likely to miss these new cases. Sharma noted that sometimes it is unclear whether patients were previously treated or not.

Treating Drug-Resistant TB

To combat MDR and XDR TB, a national DOTS-Plus committee of experts, established in 2005, developed national DOTS-Plus guidelines for India aligned with the WHO guidelines for treatment of drug-resistant TB. DOTS-Plus services for programmatic management of MDR TB were introduced as a pilot in the states of Gujarat and Maharashtra in 2007 and since then have gradually been expanded.

The model of DOTS-Plus care includes inpatient and community care. Sachdeva explained that patients are identified at the community level and then referred to the district TB officer, who collects a sample from the patient and sends it to the culture and DST laboratory. The culture and DST laboratory communicates the results to the district. The district TB officer traces the patient and sends him or her to a DOTS-Plus site for about a week for an initial workup. The patient then is placed on treatment at the DOTS-Plus site. After a week of treatment, the patient is referred back to the community, and the rest of the treatment is carried out on an outpatient basis.

The DOTS-Plus program employs a decentralized and integrated model of care. The DOTS provider at the community level sees the patient through the course of treatment. At the health facility, the doctors and paramedics

⁵ Of the 6.2 million people diagnosed with TB in 2010, 5.4 million had TB for the first time, and 0.3 million had a recurrent episode. In a small number of cases the treatment history was not recorded, and 0.4 million had already been diagnosed with TB but had their treatment changed to a retreatment regimen after treatment failure or interruption. In 2010, an estimated 3.4 percent of new TB cases globally were MDR TB and an estimated 20 percent of retreatment TB cases were MDR TB (WHO, 2011a).

⁶ Trends in global MDR TB rates remain largely unclear because of a lack of nationally representative data in many large countries, including India and several African countries (Zignol et al., 2012).

are trained to supervise the DOTS provider, as well as to manage and monitor minor side effects. At the district level, the district TB officer coordinates case findings, follow-up examinations, and reporting.

The standardized treatment regimen for MDR TB in India is a 6-drug regimen, with an intensive phase of 6–9 months and a continuation phase of 18 months; the total duration of treatment is about 24–27 months. The six drugs are kanamycin, levofloxacin, cycloserine, ethionamide, pyrazinamide, and ethambutol. P-aminosalicylic acid (PAS) is kept as a reserve drug in the event of intolerance of or a reaction to any one of the other drugs. The regimen involves daily DOT, with kanamycin given for 6 days in a week. Patients are treated according to 3 weight bands: 16–25 kg, 26–45 kg, and more than 45 kg.

In the discussion period, Sachdeva noted that because many patients were unwilling to be admitted to the hospital for a month, the period of hospitalization was reduced to about a week. Also, many MDR TB patients die in the time it takes for them to be traced, diagnosed, counseled, and put on treatment. Therefore, the goal is to diagnose patients as early as possible, in part through scale-up of the country's laboratory capacity. Another problem is that transporting sputum from patients to the culture and DST laboratories has been difficult, especially in remote areas. Accordingly, greater involvement by private-sector laboratories is being sought.

Sachdeva also noted that reports of patients with XDR TB are surfacing. Specifications for drugs for these patients are being analyzed, which will generate guidance for DOTS facilities.⁷

Procuring Drugs

The RNTCP's system of drug logistics and event-tree management is integrated with first-line anti-TB management. There are two sources of procurement: the GLC and the government of India. Quality-assured second-line drugs are being procured by the government of India with financial support from the World Bank, UNITAID,⁸ and the Global Fund,

⁷ In January 2012, following the workshop summarized herein, the emergence of TDR TB in India was reported at Hinduja Hospital in Mumbai (Udwadia et al., 2012). The reporting authors indicated that three of the four TDR TB patients had received erratic, unsupervised second-line drugs, often in incorrect doses and from a variety of private practitioners, in an effort to cure their MDR TB. The term "TDR TB" is not currently recognized by WHO or the RNTCP, which instead refer to these cases as XDR TB. For more information on this terminology, visit <http://www.who.int/tb/challenges/mdr/tdrfaqs/en/index.html> (accessed April 17, 2012).

⁸ UNITAID is an international purchase facility for medicines and diagnostics for HIV/AIDS, malaria, and TB. Started in 2006 by Brazil, Chile, France, Norway, and the United Kingdom, UNITAID generates program financing through a tax on airline tickets. Ninety-four countries currently receive UNITAID funding. For more information, visit <http://www.unitaid.eu/>.

with technical assistance from WHO and the GLC. The procurement of 23,000 drug doses for MDR TB for 2011-2012 has been initiated through the GLC and the Global Drug Facility (GDF) mechanism. Loose drugs are supplied to state drug stores and repackaged into three monthly boxes. These boxes are supplied to the districts, with loose drugs being provided to DOTS-Plus sites.

Scaling Up Laboratory Capacity

As of March 2011, India had 25 accredited culture and DST laboratories, noted Sachdeva (Figure 2-2). As of December 2010, 12 states were implementing basic DOTS-Plus services, and all planned to do so by the end of 2011. At the end of 2010, the DOTS-Plus program covered about 24 percent of the population in the 141 of the country's 658 districts that at that point had MDR TB diagnostic and treatment services available.

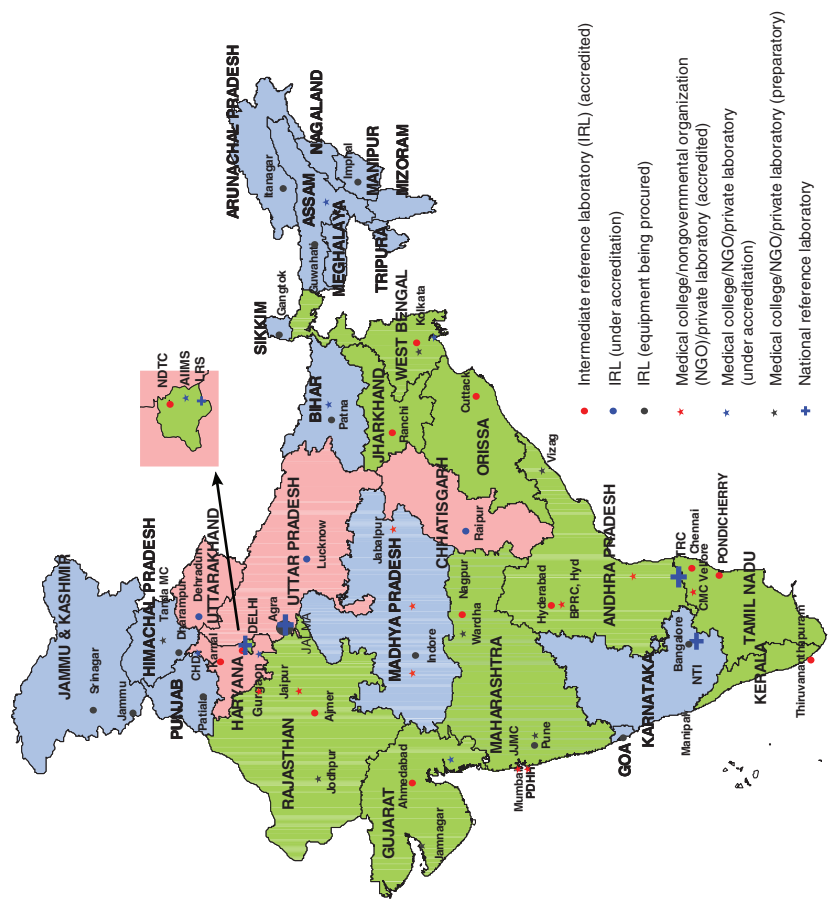
Sachdeva reported that as of December 2010, more than 19,000 patients suspected of having MDR TB had been examined and about 3,600 had been initiated on treatment. The number of patients placed on treatment has been increasing each year.

The RNTCP is currently scaling up the number of accredited culture and DST laboratories nationwide to at least 43 by 2013, with the potential for 65–70 laboratories, including private-sector and medical college laboratories, to be accredited under the program, said Sachdeva. Capacity will be increased at each laboratory through investments in sputum processing capacity, the introduction of high-throughput molecular DST, automated liquid culture systems, stronger specimen transport systems, and electronic reporting of results. By 2013, access to laboratory-based, quality-assured MDR TB diagnosis and treatment will be available to all smear-positive retreatment TB cases and new cases that have failed an initial first-line drug treatment, said Sachdeva. Also by 2013, the expected annual DST capacity will grow from 35,000 in 2010–2011 to 220,000, and at least 30,000 MDR TB patients are projected to enter treatment annually. By 2015, all smear-positive TB cases, whether new or retreatment cases, will have access to MDR TB diagnosis and treatment. UNITAID, the Global Fund, the World Bank, and WHO have all supported the laboratory scale-up effort.

Sachdeva described several components of the strategy for scaling up treatment services. Human resource capacity will be strengthened by having a DOTS-Plus coordinator in every district and additional staff at laboratories and DOTS-Plus sites. By 2012, the number of DOTS-Plus sites is slated to increase from about 24 currently to 200 sites covering all states across the country—the equivalent of 1 site per 10 million people (RNTCP Status Report, 2011). All DOTS-Plus sites will be upgraded to national airborne infection control standards. The RNTCP is advocating that drug

FIGURE 2-2 Distribution of Revised National TB Control Program (RNTCP) culture and drug susceptibility testing (DST) laboratories across India as of March 2011. As of that date, there were 25 accredited laboratories (4 national reference laboratories, 12 intermediate reference laboratories, 9 other laboratories) and 8 laboratories whose accreditation was pending. The line probe assay (LPA) was available in 4 laboratories. The RNTCP is also encouraging a number of private-sector laboratories and medical college laboratories to obtain accreditation (i.e., “preparatory” status in the legend above).

SOURCE: Sachdeva, 2011.



manufacturers adhere to WHO prequalification and GDF quality assurance programs and develop second-line drug production plans that take account of the nation's demand for the drugs. The RNTCP also is advocating with professional associations and physicians for rational use of the fluoroquinolones, especially in respiratory diseases, so that resistance to this class of drugs does not become a major challenge in the management of MDR TB.⁹ Finally, an integrated national online electronic recording and reporting system will be instituted, based on the E-TB Manager model used in Brazil.

Outcomes for patients who received standardized treatment through DOTS-Plus have been mixed, said Sharma. In a retrospective analysis of 66 patients, 53 (80.3 percent) became culture-negative, 77.3 percent of these within 3 months (Arora et al., 2007); 4 failed to convert within 9 months; and the rest died or defaulted. Among 28 patients completing 2 years of treatment, 67.9 percent were cured, 14.3 percent died, 17.9 percent defaulted, and none failed treatment. Cycloserine had to be stopped in 5 patients and kanamycin was stopped in 3 patients because of adverse effects. Other drugs were better tolerated.

By contrast, in another 2007 study of 172 MDR TB patients and 1 XDR TB patient described by Sharma, only 41.6 percent were cured, 38.7 percent failed, 15 percent defaulted, and 4.6 percent died, although this study preceded the DOTS-Plus era. During the discussion period, in response to a question about this cure rate, Sachdeva noted that many of these patients had undergone second-line treatment multiple times, and the risk of failure was greater because they were treatment experienced. Subsequent cohorts are showing better results, but they have not yet completed the full course of treatment. Earlier diagnosis and treatment could boost cure rates, said Sachdeva, but globally the treatment success rate for MDR TB is only about 60–65 percent.

Salmaan Keshavjee, Harvard Medical School, observed that a high failure rate probably points to strains that are more resistant than is commonly held. Moreover, default rates of 20 percent indicate that there is much work

⁹ At the 2010 IOM workshop in Moscow (IOM, 2011b), Peter Cegielski, CDC, shared results from the Preserving Effective TB Treatment Study (PETTS), a prospective follow-up study of MDR TB patients in nine countries aimed at determining the frequency of and risk factors for acquired resistance to second-line drugs in a diverse group of MDR TB programs. A large number of MDR TB patients already had resistance to second-line drugs at the start of treatment: 11 percent for the fluoroquinolones, 11–18 percent for injectable agents, close to 20 percent for ethionamide, and almost 10 percent for para-aminosalicylic acid. Cegielski suggested that the high level and diversity of drug resistance found at baseline suggests that standardized treatment approaches for MDR TB are not advisable. The 2010 IOM workshop in South Africa (IOM, 2011a) also included a discussion of the sensitivity of the various strains of *M.tb.* to the fluoroquinolones. Nesri Padayatchi, University of KwaZulu-Natal, shared that moxifloxacin has been one of the most commonly used fluoroquinolones for treating patients in South Africa.

to be done in India and elsewhere to strengthen the health system's capacity to deliver care. High death rates mean that greater capacity is needed to diagnose people quickly and place them on appropriate treatment. A 42 percent success rate is disturbing, he said, suggesting that the goal should be 60–80 percent. In the Tomsk prison system in Russia, for example, where inmates are resistant to all first-line drugs plus some second-line drugs, the cure rate approaches 80 percent under a collaborative DOTS-Plus program that includes the penitentiary system and the civilian health service and serves a combination of incarcerated and civilian patients, as well as vulnerable populations such as the homeless, unemployed, and disabled (Shin et al., 2006). Keshavjee explained that the reason for this success is the presence of a health system within the prison that can deliver drugs to patients each day and ensure that they take them.

Keshavjee also noted that MDR TB is a highly complex problem and that India is attempting to incorporate a complex health intervention into a health system that needs strengthening at multiple levels. Involvement of the private sector is being sought to make these efforts more feasible (see the next section and Chapter 7).

INVOLVEMENT OF THE PRIVATE SECTOR¹⁰

Indiscriminate use of anti-TB drugs, especially outside the RNTCP, has contributed significantly to the emergence of drug-resistant TB in India, said A. Kumar. In India, drugs available by prescription elsewhere are available over the counter in any pharmacy, which complicates the management of MDR TB. For example, fluoroquinolones are available over the counter and are commonly used in households for fevers and infections. In 2006, prior to the implementation of the DOTS-Plus program in India, based on the total amount of money available for anti-TB drugs sold in India, 75 percent of first-line drugs and 100 percent of second-line drugs were being used outside the RNTCP.

The National Center for Disease Control under the Indian Ministry of Health has sought to restrict the sale of anti-TB drugs without a written prescription. The Drug and Cosmetic Act of India also contains a clause restricting the sale of anti-TB drugs. A. Kumar noted that meetings organized by the GDF, WHO, and the RNTCP have brought Indian drug manufacturers together to educate them and encourage them to adhere to established standards.

An important component of the DOTS-Plus program has been the establishment of partnerships with the private sector, including nongovernmental

¹⁰ This section is based on the presentation of Ashok Kumar, Deputy Director General and Head, Central TB Division, and Project Director, RNTCP.

organizations (NGOs), medical colleges, and other private institutions. Such partnerships are critical, said A. Kumar, because it is not possible to achieve control through the actions of a single agency. The partnerships are designed to achieve community awareness, improve access to TB care, reduce patient costs and inconvenience, detect cases early, promote the rational use of anti-TB drugs, and ensure sustained funding. For example, the Indian Medical Association and other private-sector professional societies, particularly those for chest physicians, have endorsed the application of international standards of TB care.

Partners are also needed at the national and global levels. For example, Sachdeva noted that the Foundation for Innovative New Diagnostics (FIND) has aligned its work plans with India's national scale-up plan, and the Clinton Foundation has conducted an independent external validation of the national plan.

CHALLENGES TO THE REVISED NATIONAL TB CONTROL PROGRAM¹¹

India's efforts to control TB and MDR TB face a number of challenges and roadblocks, which were described by A. Kumar and Thomas.

Laboratories

For a variety of reasons, the establishment and accreditation of laboratories in some states have been delayed. The RNTCP plans to link these states with an accredited laboratory elsewhere so that services will not be affected, said A. Kumar.

Diagnosis

A. Kumar noted that conventional tests to detect drug-resistant TB are slow, tedious, and difficult to perform under field conditions. Timely availability of results is crucial for prompt patient management to reduce morbidity and mortality. Newer tools are being introduced into the RNTCP in a phased manner. The LPA, when available, is the preferred DST method in India.¹² These tools need to undergo rigorous field evaluation before they are used in populations with a significant burden of drug-resistant TB, and

¹¹ This section is based on the presentations of Ashok Kumar, Deputy Director General and Head, Central TB Division, and Project Director, RNTCP; and Aleyamma Thomas, Scientist G and Director-in-Charge, National Institute for Research in Tuberculosis.

¹² Capacity for DST with the LPA in India was less than 0.1 laboratories per 10 million population in 2010 (WHO, 2011b).

technologies that provide rapid diagnosis require staff support and training. Operational research to reduce these delays is ongoing in the state of Andhra Pradesh, supported by UNITAID.

Management

Successful management of TB patients is the responsibility of health systems, said Thomas. First-line DOTS regimens need to be followed strictly. The default rate in retreatment cases, a major source of drug-resistant TB, remains quite high. Management of drug-resistant TB is a therapeutic challenge that needs to be undertaken by experienced clinicians at centers equipped with quality-assured, accredited laboratories and inpatient and surgical facilities. Improving the efficiency with which suspected MDR TB cases are referred and tracing patients who are lost to follow-up are both critical, since the best treatment for MDR TB is to prevent it from developing. The irrational use of first- and second-line drugs needs to be discouraged, including in education and training provided at medical colleges. Patients and their relatives need to receive standardized counseling because of the long duration of treatment. And infection control measures are essential to keep the disease from spreading.

Drug Access and Supply

Ensuring an uninterrupted supply of quality-assured second-line drugs is a key issue. A. Kumar noted that the diagnostic capacity for MDR TB exceeds the number of patients who can be placed on treatment because of the limited availability of drugs. Rising costs reduce the use of these drugs. Addressing this problem will require intervention from the GLC and incentives for Indian drug manufacturers to build their capacity to produce better-quality prequalified drugs.

Human Resources

Thomas noted that the dramatic demands on program staff for supervision and treatment are posing human resource challenges in India. Staff need adequate training in management and supervision. Specifically, Thomas suggested that training should also focus on problem solving, management skills, and planning to facilitate program expansion and performance, as well as specialized training for dealing with MDR TB among vulnerable populations. Nonprogram providers and communities also need to be involved in diagnosis and management.

Data

A robust system is needed to monitor and evaluate multiple program indicators, said Thomas. Better performance will require good data collection and analysis, as well as timely dissemination of findings to end users for further improvement.

TREATMENT OF DRUG-RESISTANT TB¹³

Before 1998, most treatment of drug-resistant TB was still being provided by individual clinicians, said Sarin. These clinicians treated very few patients, and not all clinicians provided effective treatments. In 1998, WHO and international partners adopted a different strategy for dealing with the burden of drug-resistant TB, which included shifting to a community-based programmatic approach. This decision contributed to the genesis of the DOTS-Plus program, as well as the GLC.

WHO's *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis: Emergency Update* includes a hierarchy of the five groups of anti-TB drugs and instructions for building a treatment regimen (WHO, 2008, Table 7.1 and Figure 7.2):

- **Group 1**—first-line oral anti-TB drugs (isoniazid [H], rifampicin [R], ethambutol [E], pyrazinamide [Z]; rifabutin [Rfb]);
- **Group 2**—injectable anti-TB drugs (kanamycin [Km], amikacin [Am], capreomycin [Cm], streptomycin [S]);
- **Group 3**—fluoroquinolones (moxifloxacin [Mfx], levofloxacin [Lfx], ofloxacin [Ofx]);
- **Group 4**—oral bacteriostatic second-line anti-TB drugs (ethionamide [Eto], prothionamide [Pto], cycloserine [Cs], terizidone [Trd], p-aminosalicylic acid [PAS]); and
- **Group 5**—agents with unclear efficacy or an unclear role in MDR TB treatment not recommended for routine use in MDR TB patients (clofazimine [Cfx], linezolid [Lzd], amoxicillin/clavulanate [Amx/Clv], thioacetazone [Thz], imipenem/cilastatin [Ipm/Cln], high-dose isoniazid [high-dose H], clarithromycin [Clr]).

WHO (2008) also has established basic guiding principles for designing a treatment regimen for drug-resistant TB:

¹³ This section is based on the presentation of Rohit Sarin, Senior Consultant, LRS Institute of Tuberculosis and Respiratory Diseases.

- Regimens should be based on the history of drugs taken by the patient.
- Drugs commonly used in the country and the prevalence of resistance to first- and second-line drugs should be considered in developing a regimen.
- At least four anti-TB drugs that are certain, or almost certain, to be effective should be used. When evidence of effectiveness is unclear, a drug can be included in the regimen, but it should not be depended upon for success.¹⁴
- Drugs with cross-resistance should not be used. (For example, amikacin and kanamycin have high levels of cross-resistance, as do capreomycin and viomycin.)
- Adverse drug effects should be treated immediately and adequately so as to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious adverse effects.
- Drugs that are not safe in the patient should be eliminated.

Each dose of a drug is provided as DOT throughout the treatment regimen and recorded.

In addition to the above guidelines, WHO has established principles for the selection of drugs. The first is to perform DST and use a drug considered to be effective on the basis of the results. The patient should have no previous history of treatment failure with a drug and no known close contact with resistance to a drug, and drug resistance patterns should indicate that resistance to a drug is rare among the population. Finally, the regimen should include at least one injectable and one fluoroquinolone.

Drugs usually are administered at least 6 days a week. Dosage should be linked to body weight, with a preference for the higher dosage within a weight range. Injectables need to be administered for a minimum of 6 months (intensive phase), with treatment for a minimum of 18 months beyond sputum culture conversion.¹⁵

The entire regimen should be administered under DOTS, but different treatment options are available. One is an empirical treatment strategy, in which a DST report is not available, but a course of treatment is devised on the basis of a patient's history of drug intake and other factors. In an individualized treatment strategy, a DST report is available for a patient for all

¹⁴ A recent WHO (2011c) report updates this guideline to state that MDR TB treatment regimens should include at least four second-line anti-TB drugs likely to be effective, plus pyrazinamide (Z), in the intensive phase of treatment.

¹⁵ An updated WHO report (2011c) changes the guideline for duration of treatment for MDR TB patients to at least 8 months of intensive-phase treatment (an increase of 2 months relative to the 2008 guidelines). A total treatment duration of at least 20 months is recommended for MDR TB patients with no previous MDR TB treatment.

first- and second-line drugs, and the regimen is based on the susceptibility pattern. In a standardized treatment strategy, drug resistance surveillance data from representative patient populations are used to design a treatment regimen in the absence of individual drug susceptibility results. Patients in a defined group or category then receive the same standardized treatment regimen.

The advantages of a standardized treatment strategy are that the cost of the regimen is lower than that of the other two strategies, DST is not required for all drugs, the technical capacity of the physician need not be high, the regimen can be applied on a large scale, implementation is less complicated, drug ordering and training are easier, and mismanagement is less likely. The disadvantages of a standardized treatment strategy are that it is not as effective as an individualized strategy in all cases; it can amplify resistance; the drug susceptibility pattern within a community needs to be well documented; and organisms may be resistant to some of the drugs in the regimen, resulting in an avoidable increase in both cost and toxicity.

Countries can adopt MDR TB treatment strategies on the basis of the laboratory method used to confirm MDR TB. If the method involves a long time gap before results are obtained, patients can be placed on an empirical treatment regimen. If the results then demonstrate drug resistance, the patient can be placed on an individualized or standardized treatment regimen. If rapid detection methods are available, such that results are available within 1–2 days, the patient can be placed on an individualized or standardized treatment regimen as soon as results are available.

Surgery can be an adjunct to chemotherapy, but it is not indicated when the disease is extensive and bilateral. About 2 months of anti-TB therapy must be administered before surgical resection is attempted. And even with surgery, the duration of treatment still must be a minimum of 2 years.

In India, a particular treatment regimen followed as national policy is an intensive phase of 6–9 months and a continuation phase of 18 months. As specified in the DOTS-Plus guidelines, patients are monitored through sputum smears, cultures, x-rays, and some blood and laboratory investigations.

XDR TB treatment follows similar guidelines but is of longer duration since it is more difficult. A later generation of fluoroquinolones needs to be used, with greater reliance on category IV and V drugs rather than category II and III drugs; surgical resection also needs to be considered. Underlying HIV infection must be treated if present, and side effects demand comprehensive monitoring and treatment.

Predictors of success in the treatment of MDR TB are the use of pyrazinamide and ethambutol if the strain of TB is susceptible to these drugs, the use of a fluoroquinolone, the use of more than 5 drugs, sputum conversion within 2 months, and surgical resection. Predictors of failure are

previous therapy, resistance to the fluoroquinolones, resistance to injectables, the presence of cavitation, low body mass index, HIV infection, poor adherence, and positive culture at 2–3 months.

WHO also has issued recommended strategies for different programmatic situations. In India, for example, all category I failures are placed on category II treatments, and the regimen is adjusted to category IV if DST reveals drug resistance. In some countries, category I failures are started immediately on category IV treatments. In India, treatment choices for category II failures depend on results of DST and overall drug resistance patterns.

Designing treatment regimens for MDR TB is highly challenging, said Sarin. In resource-limited settings, standardized treatment regimens may be necessary instead of individualized regimens. Different options for standardized regimens are available, depending on drug resistance patterns in the country. Decisions on regimens also are linked to the availability of resources, quality-assured DST, and drugs.

IMPROVING HEALTH SYSTEM PERFORMANCE TO ADDRESS THE CHALLENGE OF DRUG-RESISTANT TB¹⁶

From 2007 to 2010, the staff of DOTS-Plus sites in India examined 19,178 MDR TB suspects, diagnosed 5,365 cases of MDR TB, and initiated treatment for 3,610 MDR TB patients (RNTCP Status Report, 2011). There is an estimated annual incidence of 99,000 cases of MDR TB in the country (RNTCP Status Report, 2011); thus, the majority of MDR TB patients are undiagnosed. Scale-up of the DOTS-Plus program is essential to increase the number of MDR TB patients receiving treatment, but strengthening of the health care system also is necessary, said Thomas. Health system strengthening is defined as an array of initiatives and strategies that improves one or more functions of the system. It leads to better health through improvements in access, coverage, quality, or efficiency. TB remains a high priority for health system strengthening, especially in view of the threat of drug-resistant forms of the disease.

With regard to human resources, Thomas continued, the goal is to have the right number of people with the right skills in the right place at the right time, who are motivated and supported to provide the right services to the right people. Health workers at all levels—from physicians and administrators to grassroots-level workers—need to be trained. Academic institutions, including medical colleges, schools of nursing, and other allied health institutions, need greater capacity. Beyond initial training, there

¹⁶ This section is based on the presentation of Aleyamma Thomas, Scientist G and Director-in-Charge, National Institute for Research in Tuberculosis.

is a need for retraining, on-the-job training, continuing education, and advanced training in management. Training in problem solving, supervision, management, and planning is needed to supplement core training in TB management. Specialized training should focus on operations research, drug management, treatment of drug-resistant TB, TB and HIV coinfection, and infection control, said Thomas.

Training should be followed by in-service monitoring and supervision to detect performance deficiencies, identify new staff in need of training, and identify additional staff needed for current and new interventions. Innovative strategies, some of which were described during the workshop (see the next section), are needed to develop the appropriate competencies to deliver services for drug-resistant TB effectively. Strategies for optimal use of shared resources and coordination of different sectors, both governmental and nongovernmental, also are needed.

Advocacy, communication, and social mobilization are important aspects of TB control, said Thomas. Policy makers and administrators should be sensitized to the need for

- adequate and sustained funding for TB control;
- sharing of resources with other public health programs;
- training of staff at different levels and retention of trained staff;
- periodic reviews to identify gaps and take corrective steps;
- communication with patients to improve adherence;
- communication with people to encourage them to demand free diagnosis and care so that TB control becomes a people's movement; and
- dissemination of the national plan for advocacy, communication, and social mobilization to field staff.

Finally, the scope for research on drug-resistant TB is broad. To improve the performance of the health system, Thomas said, research is particularly needed in the areas of

- epidemiology;
- newer tools for diagnosis and newer drugs for treatment;
- clinical trials to find ways to shorten the duration of treatment; and
- health system structure and operations, to identify constraints on the effective use of resources and quality services.

More and better research can inform evidence-based decision making at the policy level.

In conclusion, A. Kumar emphasized that antimicrobial resistance is a major threat to humanity and the fight against communicable diseases.

This vital issue requires an integrated and practical response guided by principles adopted by all countries. Without action today, there will be no cures tomorrow.

POTENTIAL INNOVATIONS AND ACTION ITEMS

Through the presentations provided in this session and the subsequent discussions, individual workshop speakers and participants noted key innovations and action items. They include the following:

- Based on lessons learned from recent Indian experience, inpatient care was reduced from 1 month to 1 week where possible.
- Because diagnoses were taking such a long time, in part because of a lack of laboratory capacity, private laboratories are now being accredited and utilized for more rapid diagnoses.
- All types of health care providers, including private-sector laboratories, NGOs, medical colleges, other private institutions, and professional societies, are now being incorporated into TB treatment.
- More and better managerial capacity in training programs for all types of health care workers is needed.
- Greater attention needs to be focused on vulnerable populations, especially pediatric populations, for whom there is currently a lack of adequate research data and information.
- Community-based care is a key strategy to reach patients early, initiate treatment, and help them stay on treatment.
- Decentralized and integrated models of care should be considered to reduce the time from diagnosis to treatment, bring treatment closer to patients, and increase the numbers of patients who complete treatment.
- An integrated national online electronic recording and reporting system will be instituted in India, based on the e-TB Manager model in Brazil.
- Advocacy, communication, and social mobilization are important aspects of TB control, and policy makers should be sensitized about the multiple needs for TB treatment.

3

The Global Burden of Drug-Resistant TB

Key Messages

- Delays in establishing strong national and international commitments to treat MDR TB aggressively have allowed the disease to spread.
- Several workshop participants noted that many high-burden countries could rapidly scale up their culture and DST laboratory capacity so that MDR TB patients can be diagnosed and placed on treatment quickly.
- Patients need quality-assured, second-line drugs at affordable prices.
- Community-based care can be preferable to hospital care if patients are being treated adequately, but care needs to be well managed in either setting.
- Many countries with high levels of MDR TB could benefit from international assistance to bridge the gap between current and needed capabilities.
- A gap between global notification of TB each year and estimated incidence indicates that many people, including people with MDR TB, are not being diagnosed and treated by current approaches.

The response to drug-resistant TB in India is occurring against the backdrop of a worldwide epidemic. An estimated 440,000 new cases of MDR TB occur annually around the world, causing an estimated 150,000

deaths (with a range of 53,000 to 170,000) (WHO, 2010b,c).¹ Failure to treat these cases adequately increases the risk of the disease spreading to others.

Salmaan Keshavjee, Harvard Medical School, presented an overview of the global profile of TB and drug-resistant TB using data provided by Matteo Zignol, STOP TB Partnership, WHO. Keshavjee also described the global challenges to effective treatment and control of drug-resistant TB, with a focus on the slow pace of treatment scale-up and the consequences of inaction. In addition, Gail Cassell, Harvard Medical School and Infectious Disease Research Institute, presented data from another high-burden country—China, which will host the fourth and last workshop in the Forum's series.

OVERVIEW OF THE GLOBAL BURDEN OF TB AND MDR TB²

According to official WHO data reported by countries in 2009, the estimated number of new cases of TB worldwide was 9.4 million, with a range of 8.9 to 9.9 million. The estimated number of deaths from TB, excluding those among HIV-positive people, was 1.3 million, with a range of 1.1 to 1.5 million (WHO, 2010b).³

About 1 in 8 cases of TB are associated with HIV—an estimated total of 1.1 million people (ranging from 1.0 to 1.2 million). Among these individuals, 380,000 deaths occur each year (ranging from 320,000 to 450,000). Overall, approximately 4,600 people die each day on average from TB, both with and without HIV coinfection.

According to WHO, the incidence of TB peaked in 2004 and has declined slightly since then. The prevalence of TB has been declining and by 2015 will be approaching, although it will not achieve, the Millennium Development Goal of half the 1990 level. With respect to mortality, the Millennium Development Goal of half the 1990 level will be achieved if the current trend continues (WHO, 2010b).

A substantial gap exists between global notifications of TB each year and estimated incidence, indicating that many people are not being reached by current approaches. The treatment success rate for regular TB has been improving—to 87 percent according to 2009 data (WHO, 2011a). How-

¹ See footnote 4 in Chapter 1 and the updated WHO (2011a) report on TB control for more information on global estimates of MDR TB.

² This section is based on slides prepared for the workshop by Matteo Zignol, STOP TB Partnership, WHO, and presented by Salmaan Keshavjee, Assistant Professor, Harvard Medical School.

³ An updated WHO (2011a) report, released after the workshop, estimates that in 2010, there were 8.8 million new cases of TB, 1.1 million deaths from TB in HIV-negative individuals, and an additional 0.35 million deaths from HIV-associated TB.

ever, this success rate varies by region and is, for example, relatively low in Europe because of the high levels of drug resistance in that region.

The proportion of MDR TB among new TB cases varies by region, with a high of more than 18 percent in the Russian Federation and some neighboring countries. Levels are high as well in some of the countries of Southeast Asia and South Asia—between 3 and 6 percent. In India, which has only subnational data, surveys point to a proportion of MDR TB among new TB cases that is within the 1.8 to 2.8 percent range (WHO, 2011b). Estimates of the proportion of MDR TB in TB retreatment cases in India range from 15 to 20 percent (WHO, 2011b). Globally, only 11 percent of the estimated 440,000 new MDR TB cases annually are reported (Keshavjee, 2011b). As noted in Chapter 2, the largest total number of estimated MDR TB cases are found in China (100,000 cases) and India (99,000 cases), followed by Russia (38,000 cases) (WHO, 2010b). Most countries had reported at least one case of XDR TB by the end of March 2011. The global proportion of XDR TB among MDR TB cases was 9.4 percent (confidence interval: 7.4–11.6 percent) (Zignol et al., 2012). The proportion of reported versus estimated MDR TB cases varies widely by region (Table 3-1).

Laboratory capacity to diagnose TB is insufficient in many of the 36 countries with a high burden of TB, MDR TB, or HIV. Twenty-seven high-burden countries have fewer than one smear microscopy laboratory per 100,000 population. Diagnosing drug-resistant TB requires culture and DST capacity, with a minimum standard set by WHO of at least one culture laboratory per 5 million population and one DST laboratory per 10 million population. Very few high-burden countries have this capacity.

Finally, treatment outcomes vary from country to country. Kazakhstan has shown a treatment success rate for MDR TB of around 75 percent, while Brazil, South Africa, and Romania have success rates below 50 percent (WHO, 2010b). In some cases, low success rates are due to a failure

TABLE 3-1 Estimated Versus Reported MDR TB Cases in 2009

WHO Region	Estimated	Reported	Ratio (%)
African	69,000	10,735	16
American	8,200	2,795	34
Eastern Mediterranean	24,000	480	2
European	81,000	28,240	35
Southeast Asian	130,000	2,549	2
Western Pacific	120,000	2,057	2
Global	440,000	46,856	11

SOURCE: Keshavjee, 2011b.

to perform sufficient evaluations rather than actual failure rates. In other cases, however, failure and death rates are in fact high.

A striking feature of surveillance results for drug resistance is the high levels of resistance to the fluoroquinolones in some regions. In Belgium, a quarter of 31 patients tested showed fluoroquinolone resistance. In Latvia, 16 percent of 258 patients tested showed resistance. Rates were 14 percent in South Africa, 29 percent in Azerbaijan, 12.5 percent in Armenia, and 27.4 percent in China (WHO, 2011b). In India, recent statewide surveillance of drug-resistant TB in the state of Gujarat showed resistance to fluoroquinolones in 24 percent of TB cases (19 percent among new and 25 percent among previously treated cases) (Mohapatra, 2010; Ramachandran et al., 2009). These are troubling findings, since the fluoroquinolones are the backbone of second-line treatment regimens (see Chapter 2 for a description of treatment regimens and anti-TB drug classifications).

MDR TB PREVENTION AND CONTROL IN CHINA⁴

Depending on the 2007–2008 baseline survey of drug resistance used, it is estimated that China has 120,000 new MDR TB cases and 9,000 new XDR TB cases annually. Among new TB cases, 5.71 percent are MDR TB and 0.47 percent XDR TB. Among retreatment cases, the corresponding proportions are 25.6 and 2.06 percent, and for all cases, they are 8.32 percent and 0.68 percent.

These rates vary greatly by province. The proportion can be as high as 10.8 percent for new cases and 41.9 percent for retreatment cases. The overall rate of MDR TB in China among all TB cases ranges from 3.5 to 23.3 percent, depending on the province.

China has embarked on a Global Fund pilot project to control MDR TB that incorporates enhanced service system and management mechanisms. As of December 2010, this project had covered 41 prefectures in 12 provinces and had confirmed 1,978 MDR TB cases, with 1,049 patients enrolled in treatment. The sputum conversion rate was 75.6 percent at the end of 6 months, and the culture conversion rate was 65.2 percent.

As part of a Gates Foundation initiative, China also is exploring rapid diagnosis; creating a standardized medical service package; establishing funding mechanisms that consist of multiple streams (including government funding and health insurance); and creating models for disbursement, supervision, and collaboration between hospitals and the country's

⁴ This section is based on slides prepared for the workshop by Mingting Chen, National Center for Tuberculosis Control and Prevention of China, and presented by Gail Cassell, Visiting Professor, Harvard Medical School, and Vice President of TB Drug Discovery, Infectious Disease Research Institute.

Center for Disease Control. Progress on MDR TB control constitutes a major national science and technology project and includes operational, biological, and epidemiological research. Technical preparation includes the development and issuance of guidelines for MDR TB chemotherapy and for infection control.

The National Action Plan in China calls for reducing the number of MDR TB cases through both prevention and control. The prevention plan includes consolidation and enhancement of the strategy for DOTS implementation, increased accessibility and equalization of general TB control services, the production of quality-assured anti-TB drugs, standardized use and management of the drugs, and reinforced infection control measures. The control plan includes guaranteeing complementary government funding of the Global Fund project and further exploring and expanding the Gates MDR TB project.

Finally, China is strengthening its laboratory capacity to fulfill its National Development Plan, to implement accreditation, to establish regional reference laboratories, and to strengthen training and increase cadres of eligible staff. China also is expanding culture capacity at the county level and DST capacity at the prefecture level and introducing new diagnostics at multiple levels.

HISTORICAL PERSPECTIVE ON TB AND MDR TB CONTROL EFFORTS

The slow pace of treatment scale-up across the globe has affected MDR TB for decades, Keshavjee observed. However, the reversal of a TB epidemic in New York City in the late 1980s and early 1990s illustrates what can be done with resources, leadership, political will, and the implementation of well-designed public health programs. Fueled by poverty, homelessness, AIDS and other diseases, and the erosion of the city's public health infrastructure, 4,000 cases of TB were reported in 1991—a 152 percent increase over 1980 (IOM, 2011b). The New York City Health Commissioner at the time, Margaret Hamburg, drew upon the strong political will of the mayor and others to gather resources and mobilize a comprehensive response to the resurgence of TB in the city. The city increased the number of patients receiving DOT and increased screening, monitoring, and isolation capacity in hospitals, shelters, and other congregate settings. These efforts effectively turned the epidemic around—TB cases in the city dropped by almost 46 percent and drug-resistant cases by 86 percent between 1992 and 1997 (IOM, 2011b). In 1995, a report called further attention to the TB epidemic in New York City and the steps completed to combat the problem successfully (Frieden et al., 1995).

On the global stage, however, a report from WHO (1996) stated that

“MDR TB is too expensive to treat in poor countries; it detracts attention and resources from treating drug-susceptible cases.” Moreover, WHO indicated that DOTS alone would be able to bring drug resistance under control. This position was based on the mistaken notion that drug-resistant strains were less fit and would eventually disappear if short-course chemotherapy was administered effectively, Keshavjee noted.

In August 1996, Partners In Health and Harvard Medical School, together with the Peruvian National TB Program, initiated a large-scale, community-based program to combat drug-resistant TB in the Northern Cone of Lima—the first program of its kind in any poor country. At the time, Lima had a strong DOTS program, but treatment approaches overall were weak. Physicians were prescribing drugs outside the system, and drug resistance was running at 2.5 to 3 percent, according to Keshavjee. Resistance was concentrated among poor people and in slums, where it was difficult to deliver care and where access to second-line drugs was limited. Working with the government, Partners In Health purchased the necessary drugs and mobilized community health workers (CHWs) to deliver care, demonstrating that community-based delivery of MDR TB treatment is feasible in resource-limited settings.

It took another decade, until 2006, for WHO to adopt this model and incorporate it into the WHO TB guidelines. There was a lag of about 15 years or more between when it was known that MDR TB could be treated and when its treatment even in resource-limited areas became global policy. As a result, there was during that period very little investment in laboratory infrastructure and in the comprehensive delivery systems required to treat patients.

The good news, said Keshavjee, is that in 2009 the World Health Assembly approved a resolution urging all member states to “achieve universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis as part of the transition to universal health coverage, thereby saving lives and protecting communities” (WHA, 2009). The resolution also called for:

a comprehensive framework for management and care of multidrug-resistant and extensively drug-resistant tuberculosis that includes DOT, community-based and patient-centered care, and which identifies and addresses the needs of persons living with HIV, the poor and other vulnerable groups, such as prisoners, mineworkers, migrants, drug users, and alcohol dependants, as well as the underlying social determinants of tuberculosis and multidrug-resistant and extensively drug-resistant tuberculosis.

Policies have finally changed, said Keshavjee, but for more than a decade, untreated patients were infecting other patients. “By leaving this

disease untreated for that decade plus, untold amounts of damage have happened globally, and now we are in a real quagmire,” he said.

GLOBAL CHALLENGES AND POTENTIAL SOLUTIONS⁵

Keshavjee discussed several global challenges faced in addressing drug-resistant TB: inadequate diagnostic capacity, an inadequate drug supply, inadequate capacity to deliver care, and inadequate international assistance.

Inadequate Diagnostic Capacity

To diagnose MDR TB, rapid culture testing and DST are essential, Keshavjee stressed. Today, liquid bacterial culture can provide results in about 2 weeks, while molecular tests can provide results in 2 hours to 2 days. Both types of tests have limitations: liquid and culture tests require extensive laboratory infrastructure, while molecular tests can be limited because they are designed to look only for the presence of specific genes. However, suggested Keshavjee, molecular tests are “a step in the right direction.” One of the newest testing technologies, GeneXpert, may require less extensive infrastructure, but time will tell whether that is in fact the case.

A major need, even with GeneXpert, is a test that works with children and people with HIV, said Keshavjee. Both represent large proportions of people with TB, but TB can be difficult to diagnose in these patients, and they are at the highest risk of death. There also has been little movement toward true rapid point-of-care diagnostics that would enable people to be diagnosed by their care provider and begin treatment immediately after testing.

India and other countries are demonstrating how testing capacity can be built. Keshavjee cited the example of Lesotho in southern Africa, where the rate of TB is about 600 per 100,000 population, about 1,000 new MDR TB cases occur per year, and a quarter of the population is HIV-positive (Paramasivan et al., 2010). Between 2006 and 2008, with support from FIND, basic laboratories that performed only smear testing were converted at a cost of less than \$500,000 into laboratories that could perform rapid liquid culture testing (Paramasivan et al., 2010). More recently, laboratories in Lesotho have been able to perform molecular testing, patients can receive results in less than 2 hours, and the general approach is being implemented in many other countries through the Expanding Access to New Diagnostics for TB (EXPAND-TB) program. “The Lesotho example demonstrates what

⁵ This section is based on the presentation of Salmaan Keshavjee, Assistant Professor, Harvard Medical School.

can be done in resource-limited settings with a little bit of money and a good plan,” said Keshavjee.

Inadequate Drug Supply

The second major challenge after inadequate diagnostic capacity is an inadequate drug supply. The creation of the DOTS-Plus program raised the question of how patients would receive needed drugs, given their expense and unavailability in many countries. In response, Jim Kim and colleagues at Partners In Health and Harvard Medical School created the GLC, together with key stakeholders such as Médecins Sans Frontières, KNCV Tuberculosis Foundation, IUATLD, CDC, and WHO. The GLC has a threefold mandate: (1) ensure access to quality-assured second-line TB drugs at affordable prices, (2) monitor and evaluate the use of second-line drugs in approved projects, and (3) promote technical assistance for MDR TB programs in keeping with WHO guidelines.

The work done by the GLC had “amazing” results, according to Keshavjee, in terms of reducing the prices of second-line TB drugs necessary to treat MDR TB. Between 1997 and 2000, prices for second-line drugs declined by 84 to 98 percent (Table 3-2) as a result of negotiations based on GLC plans for pooled procurement of drugs. Although drug prices remain high in some places, they were much higher before the GLC existed.

Despite the success in reducing prices for some drugs, the number of manufacturers of quality-assured second-line drugs remains inadequate, Keshavjee noted. Procurement is not pooled, eliminating the downward pressure on prices that pooled procurement would produce. The market has been opaque, with insufficient forecasting to provide assurance about future markets. Prices remain very high for some drugs, and delivery delays can be severe. The system for providing drugs remains centralized, and countries prefer to do business with local manufacturers.

TABLE 3-2 Reduced Prices of Second-Line TB Drugs (1997–2000)

Drug	Formulation	1997 Price (USD)	2000 Price (USD)	% Decline
Amikacin	1 gm vial	9.00	0.90	90
Cycloserine	250 mg tab	3.99	0.50	87
Ethionamide	250 mg tab	0.90	0.14	84
Kanamycin	1 gm vial	2.50	0.39	84
Capreomycin	1 gm vial	29.90	0.90	97
Ofloxacin	200 mg tab	2.00	0.05	98

SOURCE: Keshavjee, 2011a.

TABLE 3-3 Prices for Green Light Committee-Approved Drugs

Drug	Price in July 2001 (USD)	Price in March 2011 (USD) (lowest price)	% Difference 2001–2011
Amikacin 500 mg	0.11	1.20	+991
Kanamycin 1 g	0.36	2.58	+617
Cycloserine 250 mg	0.14	0.59	+321
Capreomycin 1 g	1.02	4.00	+292
Ethionamide 250 mg	0.10	0.09	Stable
Prothionamide 250 mg	0.10	0.10	Stable
P-aminosalicylic acid (PAS) 4 g sachet	1.51	1.57	Stable

SOURCE: Médecins Sans Frontières (MSF) and the International Union Against Tuberculosis and Lung Disease (The Union). 2011. *DR-TB Drugs Under the Microscope: Sources and Prices for Drug-Resistant Tuberculosis Medicines*. <http://www.msfaaccess.org/content/dr-tb-drugs-under-microscope> (accessed November 16, 2011). This table has been adapted from the original table in the report.

Furthermore, although competition would typically lower prices and allow affordable access to medical technologies, second-line anti-TB drugs have been an exception. “The more we have bought, the higher the price has gone,” Keshavjee said. The standard 18- to 24-month treatment course for MDR TB, using drugs procured through the GLC, costs between \$4,400 and \$9,000 per patient (MSF and IUATLD, 2011). Prices for some drugs rose substantially between 2001 and 2011 (Table 3-3), with little economic explanation for the rise, according to Keshavjee. New mechanisms for providing access to drugs need to be explored, and new drugs now being developed could help. At the same time, however, getting both old and new drugs to patients remains a major problem (see Chapter 8 for a discussion of the supply chain for second-line MDR TB drugs).

Inadequate Capacity to Deliver Care

Many countries lack the systems needed to deliver care to patients and to manage adverse events over the 2-year period of treatment. In addition, said Keshavjee, systems are needed to help countries rapidly scale up their care delivery capacity. Infection control also must be made a priority in all treatment settings, even in areas with a weak health care system. People working in health facilities need respirators, and the facilities need proper ventilation when they contain inpatients.

Most countries with many TB patients lack sufficient hospital beds, so patients must be treated outside the hospital. This can be an advantage, said Keshavjee, in that ambulatory care costs less, freeing resources to treat

more patients. Moreover, it is safer if patients are not concentrated in small spaces (such as hospital wards) where drug-resistant TB can spread.

Community-based treatment also is preferable for TB patients, including MDR TB patients, who live away from major cities. Such patients generally cannot travel regularly to a distant facility for treatment, so trained CHWs must go to patients' houses to treat them. Treating all patients wherever they are is the most effective way to change the dynamics of the epidemic, suggested Keshavjee.

Inadequate International Assistance

Many countries need help to bridge the gap between current capabilities and what is needed, yet international technical assistance is inadequate, Keshavjee emphasized. Successful regional MDR TB treatment programs have shown what can be done with on-site long-term technical assistance and, where necessary, on-site implementation teams. Such teams may be provided for countries, or countries may create their own teams.

Most countries that face problems with drug-resistant TB are relatively poor, with a large proportion of their populations living on less than \$2 a day. As K. Srinath Reddy, Public Health Foundation of India, observed in his keynote address (Chapter 1), it is difficult or impossible to institute a strong anti-TB program within a weak health system. Today, a growing number of sites and countries have had experience with helping others scale up anti-TB programs. These centers of excellence can act as hubs for implementation by providing in-country support teams and helping other countries scale up.

The alternative to strong action is clear, said Keshavjee. For example, in parts of the former Soviet Union where he has worked, more than 25 percent of all TB patients have MDR TB, and XDR TB remains a growing threat. The global approach being taken today remains hampered by constrained structures and a lack of innovative thinking. Engagement with key partners, such as PEPFAR, UNICEF (United Nations Children's Fund), UNDP (United Nations Development Program), and others, has been lacking, and a focus on implementation, the involvement of the private sector, and advocacy in countries have been limited.

POTENTIAL INNOVATIONS AND ACTION ITEMS

Through the presentations provided in this session and the subsequent discussions, individual workshop speakers and participants noted key innovations and action items. They include the following:

- Community-based treatment is often preferable to improve the efficiency and effectiveness of treatment, and it benefits TB patients who live away from major cities.
- A comprehensive framework for management and care of MDR and XDR TB would improve the effectiveness and efficiency of treatment. A comprehensive framework would also include vulnerable populations.
- On-site long-term technical assistance and on-site implementation teams from within a given country or drawn from regional and international expertise can improve MDR TB treatment programs.

4

Preventing Transmission of Drug-Resistant TB

Key Messages

- Global estimates indicate that approximately half of new MDR TB cases are occurring in people who have not been treated previously, indicating transmission of the disease (Nardell and Dharmadhikari, 2010; WHO, 2010c).
- The ongoing development of effective infection control policies offers many opportunities to reduce the transmission of MDR TB in India.
- Rapid diagnosis of MDR and XDR TB is key to initiating treatment as quickly as possible and isolating patients so they cannot infect others.
- MDR TB patients can be treated in the community with confidence as long as they are receiving the appropriate therapy.
- Drug-resistant strains of *M.tb.* can undergo mutations that make them less fit than drug-susceptible strains, but they also can undergo additional mutations that compensate for this lost fitness.
- Unsuspected TB and MDR TB patients are the groups most likely to transmit infection to others. If DST could be completed quickly and early, patients could be treated immediately and transmission of disease reduced.
- Measures to strengthen infection control efforts, including through reduced length of inpatient care and provision of community-based treatment, are key to reducing the transmission of MDR TB.

According to WHO estimates, approximately half of new cases of MDR TB appear to occur through transmission, not through inadequate management of preexisting infection (Nardell and Dharmadhikari, 2010; WHO, 2010c). Infection control is therefore a vital consideration in any national program to control drug-resistant TB. Presentations on this topic addressed some of the steps India is taking to prevent transmission of MDR TB, the potential for drug-resistant TB to spread both in health care institutions and in the community, the evolutionary forces that shape fitness in *M.tb.*, and the contributions molecular epidemiology can make to understanding the spread of drug-resistant TB.

INDIA'S PROGRAM EFFORTS TO PREVENT TRANSMISSION OF DRUG-RESISTANT TB¹

India's program efforts to prevent transmission of drug-resistant TB include the development of infection control guidelines, strengthening of laboratory capacity, and rational use of anti-TB drugs.

Infection Control Guidelines

TB infection control has historically been problematic in India, said Prahlad Kumar, Director, National Tuberculosis Institute-Bangalore. Guidelines for airborne infection control have been lacking. Most health care facilities have been overcrowded, and hospital administrations generally have not been committed to infection control. Additional challenges have been the high TB burden, vulnerable populations, and the need for scale-up of response and coordination.

At the same time, there are many opportunities to improve infection control in India, including the strengthening of the health system now under way, lessons learned in confronting pandemic influenza, growing awareness of the importance of infection control, and efforts by hospitals to gain accreditation. P. Kumar cited three examples of efforts to improve infection control in India: (1) the National Airborne Infection Control Committee has developed and pilot tested national guidelines for airborne infection control; (2) the RNTCP is upgrading infection control measures at DOTS-Plus indoor facilities; and (3) infection control measures are being implemented in the intermediate reference laboratories.

The national guidelines developed by the National Airborne Infection Control Committee provide up-to-date information on recommended methods for reducing the risk of airborne infections in health care facilities.

¹ This section is based on the presentation of Prahlad Kumar, Director, National Tuberculosis Institute-Bangalore.

The target audiences are health facility administrators and infection control focal points. The guidelines, which were adapted from the WHO infection control policy of 2009, cover managerial activities; administrative, environmental, and personal protective measures; special settings; household settings; airborne infection control risk assessment; and quarterly reporting systems.

One objective of the pilot testing is to conduct systematic baseline assessments of infection control and administrative, environmental, and personal protective measures and practices at 35 selected health care facilities in three Indian states. Another objective is to offer state and district officials and administrators focal points for capacity building, specific recommendations, and supportive supervision on a limited basis. The translation of the pilot to practice will involve follow-up assessments, revision of national guidelines based on the feasibility and effectiveness of the measures implemented, integration of infection control into hospital accreditation and routine health system reporting, and integrated infection control training materials for front-line health care workers.

Strengthening of Laboratory Capacity

Four national reference laboratories—the National Institute for Research in Tuberculosis, Chennai; the National Tuberculosis Institute in Bangalore; the LRS Institute in New Delhi; and the Central Jalma Institute for Leprosy and Other Mycobacterial Diseases in Agra—are working closely with intermediate reference laboratories, medical college laboratories, and private laboratories. The stakeholders and partners meet on a quarterly basis to share their experiences. Newer diagnostic tools also are being evaluated, with scale-up planned for those found to be effective.

Rational Use of Anti-TB Drugs

The rational use of anti-TB drugs has been a problem in India. A substantial quantity of first-line anti-TB drugs² and almost 100 percent of second-line anti-TB drugs have been sold and used outside the RNTCP. Management of TB patients outside the RNTCP often is poor, leading to the risk of treatment failure and the development of drug resistance.³ The large and unregulated private sector has a conflict of interest with respect

² According to 2006 data, the private sector accounted for the purchase of 74 percent (\$69.7 million) of India's total drug market for first-line anti-TB drugs; the remaining one-quarter of the drug market was accounted for by public-sector purchasing (TB Alliance, 2007).

³ A survey of 106 private practitioners in Mumbai found that only 6 of 106 practitioners wrote a correct prescription for the treatment of drug-susceptible TB, and only 3 of the 106 wrote an appropriate treatment regimen for MDR TB (Udwadia et al., 2010).

to better TB management because it profits from the easy availability of anti-TB drugs.

The Chennai Consensus Statement, developed by a broad range of stakeholders, called for all people involved in TB care to implement international standards of care. In addition, the Indian Medical Association, on behalf of the RNTCP, collaborated with the Medical Council of India to draft guidelines for the rational use of anti-TB drugs. Discussions were conducted to establish additional prequalified drug manufacturers and the implementation of WHO standards.

THE IMPACT OF TREATMENT ON MDR TB TRANSMISSION⁴

As noted above, more than half of new MDR TB cases are occurring in people who have not been treated previously. Many new cases therefore are resulting from transmission, not from poorly managed treatment. For that reason, treating MDR TB cases in hospitals can be a risk factor for transmission, and minimizing the time patients are in hospitals is desirable, said Edward Nardell, Harvard Medical School.

Community-based MDR TB treatment programs, which now exist in many parts of the world (e.g., Cambodia, Ethiopia, Haiti, Lesotho, Pakistan, Peru [Shin et al., 2004], Russia, South Africa [Heller et al., 2010], and Swaziland), may also appear to raise concern about transmission. But Nardell said that if community-based treatment is implemented well, transmission probably is not a major concern.

For many years, 14 days was viewed as the necessary period of isolation for patients with drug-susceptible TB once treatment had been initiated. This time period was not based on patients having negative cultures, which can take much longer than 14 days to achieve. Rather, it appeared to be based on several studies dating back to 1960 regarding the effects of chemotherapy on transmission.⁵ Rouillon and colleagues (1976) concluded that smear positivity and culture positivity correlate with transmission before but not after therapy has begun. They went on to write, "There is an ever-increasing amount of evidence in support of the idea that abolition

⁴ This section is based on the presentation of Edward Nardell, Associate Professor of Medicine, Harvard Medical School.

⁵ For example, Andrews and colleagues (1960) showed that household conversions did not occur after the start of treatment, so people could be sent home rather than being kept in the hospital. Brooks and colleagues (1973) found 107 tuberculin skin test (TST)-negative subjects living with 19 patients with active TB, yet there were no TST conversions in the contacts after the beginning of treatment. A later review of these early studies found fault with many of them (Menzies, 1997). In some cases, for example, less infectious patients may have been selected for home treatment, or uninfected household contacts may have been less susceptible. Menzies concluded that smear-positive patients should still be considered infectious after 2 weeks.

of the patient's infectiousness—a different matter from 'cure,' which may take months, and from negative results of bacteriological examinations, direct and culture, which may take weeks—is very probably obtained after less than two weeks of treatment." The 14-day period appears to be based on this assumption—that 2 weeks of treatment is sufficient to abolish infectiousness—said Nardell. This assumption led to the revision of guidelines for when patients could be discharged from the hospital, when they could go back to work, and when they were no longer a public health threat.

In the classic experiments of Richard Riley in the 1950s, patients with strongly positive smears and cavitary TB in hospital rooms in Baltimore were connected by way of the ventilation system to hundreds of sentinel guinea pigs that occupied cages in the penthouse above the clinical ward (Riley et al., 1959). Only 3 of the 77 patients produced 35 of 48 (73 percent) of the guinea pig infections that were observed. The guinea pig infections tended to occur when patients with drug-resistant TB on inadequate therapy were admitted to the ward. When drug-susceptible patients were admitted to the ward and started on treatment the same day, no guinea pig infections occurred. Compared with some patients who were left untreated for a time to gauge their infectiousness, treatment started the same day as admission was shown in other patients to be dramatically effective in preventing transmission to the guinea pigs. Drug-resistant patients were somewhat less infectious, suggesting the existence of a fitness deficit in their strains of *M.tb*. Riley concluded from these experiments that decreases in infectiousness resulting from treatment preceded the elimination of the organisms from the sputum (Riley et al., 1962). Later it was speculated that when people cough, large particles evaporate as they settle (Loudon et al., 1969). The drug in these secretions then is concentrated and inactivates the infectious agent. With sputum cultures, in contrast, there is no evaporation, and growth support is optimized.

A recent similar study from Peru found that almost all the transmission that occurred on a TB ward was due to 9 unsuspected and inadequately treated MDR TB patients among 97 HIV-positive pulmonary TB patients, to whom 292 guinea pigs were exposed over 505 days (Escombe et al., 2008). Only 3 guinea pigs were infected by drug-susceptible patients, but all of those patients had undergone intermittent or delayed treatment.

In Nardell's similar experiments in South Africa, 360 guinea pigs were exposed over the course of 4 months to 109 smear-positive, cavitary, and coughing TB patients recently initiated on therapy. All of the infections in the guinea pigs were due to XDR TB patients who were not being treated for XDR TB. When none of the patients had XDR TB, virtually no transmission occurred. Nardell concluded that in that experiment, standard South African treatment for MDR TB starting on the day patients entered

the hospital, not 2 weeks before, completely suppressed transmission in the 27 patients studied.

With respect to household contacts of MDR TB patients, at least half of those who contract the disease are infected with a strain that does not match that of the index case, suggesting that there are opportunities for transmission outside the home. In addition, only about one-third of pulmonary TB patients infect even close contacts, although household contacts would be the highest priority for active case finding.

From these observations, Nardell concluded that unsuspected TB patients, whether drug-susceptible or drug-resistant, are the group most likely to be transmitting infection to others. Thus, if India performed DST only on people who had failed treatment, those patients could be in the hospital for 3–4 months transmitting TB before DST results showed that they were drug-resistant. Similarly, in MDR TB wards, unsuspected XDR TB patients would be the group transmitting the disease.

Thus, rapid diagnosis of TB, MDR TB, and XDR TB is essential for patients to be treated so they cannot infect others. Those who are drug-susceptible or have MDR TB can be treated in the community with confidence as long as they are receiving the appropriate therapy. But if DST is not performed early and quickly, people may transmit for months before they are identified as drug-resistant. Nardell highlighted the need to find TB cases actively based on cough surveillance, perform rapid specific diagnosis using GeneXpert, separate cases safely while they are awaiting diagnosis and treatment, rule out XDR TB, and treat effectively based on DST and using a secure supply of quality-assured drugs. Prompt diagnosis of drug resistance and prompt therapy are critical, whether in the hospital or in the community.

It is unclear whether the drugs available for XDR TB, which by definition excludes the fluoroquinolones, are effective in halting transmission. It may be that XDR TB requires prolonged isolation while the patient is still coughing. Nardell noted that XDR TB patients are a far smaller group of patients to isolate than all TB and MDR TB patients, who can be treated safely in the community.

THE GENETIC EVOLUTION OF *M.tb.*⁶

Evolutionary thinking is critical in considering the future of MDR and XDR TB, said Sébastien Gagneux, Unit Head and Assistant Professor, Swiss Tropical and Public Health Institute and University of Basel. The future of MDR and XDR TB depends largely on the fitness of the organisms that

⁶ This section is based on the presentation of Sébastien Gagneux, Unit Head and Assistant Professor, Swiss Tropical and Public Health Institute and University of Basel.

cause the disease, which is determined by their virulence and transmissibility. Biologists have long thought that drug-resistant strains of *M.tb.* are less transmissible and virulent than drug-susceptible strains, a conclusion dating back to studies done in the 1950s that measured the virulence of isoniazid-resistant strains in guinea pigs. Because at least some of the drug-resistant strains were less virulent, a large proportion of the TB community thought at the time that drug resistance was not a major public health problem.

Fitness can be measured in many different ways, such as through virulence in guinea pigs or molecular epidemiological studies that measure the generation of secondary cases. Depending on the strain being studied and the definition of fitness used, the measured fitness of drug-resistant strains of *M.tb.* compared with that of drug-susceptible strains varies from 10 times more to 10 times less fit (Borrell and Gagneux, 2009). In other words, drug-resistant TB strains are not going away, Gagneux said.

Experiments have shown that the development of resistance in most cases does cause a drop in fitness. Today, drug-resistant strains account for only 3 percent of 10 million new cases of TB each year, even though TB has been treated for at least 50 years with drugs. However, the less fit bacteria can undergo additional mutations over time that compensate for the initial fitness defect. Also, not all mutations that cause drug resistance have an effect on fitness. Some strains can have a genetic background in which some mutations can confer drug resistance without reducing fitness. For example, the Beijing strain, which has been associated with drug resistance in many places, may be preadapted to deal with the potential fitness cost of resistance, Gagneux said, although this idea remains merely a reasonable hypothesis today.

The interactions between mutations and genetic background are termed *epistatic* interactions, and they have been studied very little in *M.tb.* In *E. coli*, however, experiments using streptomycin, quinolones, and rifampicin have shown that double mutants can have better fitness than single mutants (Trindade et al., 2009). This so-called positive epistasis suggests that one mutation can drive fitness down, but a second mutation can at least partly compensate for the defect while simultaneously conferring resistance to a second drug.

In a study of laboratory and clinical strains of *M.tb.*, Gagneux and colleagues (2006) found that mutations in the laboratory strains all had a statistically significant fitness defect, although the effect varied by strain and mutation. When drug-resistant strains from TB patients were compared with drug-susceptible counterparts from the same patients, however, at least some of the drug-resistant strains showed no fitness loss. The authors hypothesized that the clinical strains had undergone additional mutations over time that compensated for the initial fitness cost. Gagneux's laboratory is now testing this hypothesis using a combination of experimental

evolution and whole genome sequencing. In addition, epistasis as has been observed in *E. coli* needs to undergo much further study in *M.tb.*, said Gagneux. The phenomenon is not straightforward, but it is important to understanding the future of drug resistance around the world.

THE MOLECULAR EPIDEMIOLOGY OF *M.tb.*⁷

According to S. Siva Kumar, Technical Research Assistant, National Institute for Research in Tuberculosis, molecular epidemiological studies are essential to efforts to curtail the epidemic of TB and MDR TB. Molecular epidemiology combines molecular biology, clinical medicine, statistics, and epidemiology. It focuses on the role of genetic and environmental risk factors at the molecular, cellular, and biochemical levels in the etiology and distribution of a disease or pathogen.

In the case of *M.tb.*, molecular epidemiology uses a multidisciplinary approach to analyze the dynamics of transmission, mainly by contact tracing. It also is useful in dividing recurrent TB into two types. The first is endogenous reactivation, in which latent TB reinfects an individual and leads to disease after a previous episode of TB has been clinically cured. The second is exogenous reinfection, in which a person becomes reinfecting with a new strain of *M.tb.* In addition, molecular epidemiology studies are important in detecting laboratory cross-contamination, identifying hyper-virulent strains circulating in a population, investigating the evolution of *M.tb.*, evaluating TB-control programs, and monitoring the transmission of drug resistance.

Three methods are widely used for molecular epidemiology focused on TB. IS6110 restriction fragment length polymorphism typing detects the variable occurrence of a 1,335 base pair genomic repeat in different strains of the bacterium. Spoligotyping measures the occurrence of a 36 base pair repeat and spacers between those repeats in a particular region of the bacterium's genome. Finally, MIRU-VNTR typing examines the variable number of tandem repeats (VNTR) within mycobacterial interspersed repetitive units (MIRU). Other methods used for typing *M.tb.* are polymorphic GC-rich sequence analysis, genomic deletion analysis, use of strain-specific markers for rapid diagnosis of the strain prevalent in an area, and single-nucleotide polymorphism analysis.

Using IS6110 RFLP analysis and spoligotyping, Shanmugam and colleagues (2011) investigated the distribution of different genotypes of *M.tb.* in the Tiruvallur region of South India and their association with drug resistance. They divided 1,650 samples into two broad categories: the East

⁷ This section is based on the presentation of S. Siva Kumar, Technical Research Assistant, National Institute for Research in Tuberculosis.

African-Indian (EAI) group and the non-EAI group. The EAI group can be divided into six subgroups, with EAI 3 and EAI 5 being common in this area of South India. Other strains found in South India are Beijing, Central Asian (CAS), and Haarlem. In South India, the EAI group predominates, whereas in North India, the CAS and Beijing strains predominate. Among the MDR TB strains, the Beijing and CAS strains are most abundant at 12.8 and 11.4 percent, respectively. The EAI strains in South India are less prone to drug resistance than the other strains.

When spoligotypes were compared with treatment regimens, no difference was found in the strain distribution among patients undergoing category I, II, and III treatment. In the category II cases, however, a higher percentage of drug resistance was seen.

In a second study, Narayanan and colleagues (2010) looked at the type of TB recurrence among HIV-infected and HIV-uninfected patients. Using IS6110, spoligotyping, and MIRU-VNTR, they found that exogenous reinfection was 88 percent and endogenous reactivation was 12 percent in HIV-infected patients. In contrast, in HIV-uninfected patients, endogenous reactivation was 91 percent, compared with an exogenous reinfection rate of 9 percent. Understanding these rates of recurrence and reinfection is essential to preventing the spread of MDR TB, said Siva Kumar.

POTENTIAL INNOVATIONS AND ACTION ITEMS

Through the presentations provided in this session and the subsequent discussions, individual workshop speakers and participants noted key innovations and action items. They include the following:

- Evolutionary thinking is critical in considering the future of MDR and XDR TB. The future of MDR and XDR TB depends largely on the fitness of the organisms that cause the disease, which is determined by their virulence and transmissibility.
- There is a need to find TB cases actively based on cough surveillance, perform rapid specific diagnosis using GeneXpert, separate cases, rule out XDR TB, and treat effectively based on DST and using a secure supply of quality-assured drugs.

5

Detecting Drug Resistance and Strengthening Laboratory Capacity

Key Messages

- New diagnostic technologies require both performance assessments and quality assurance to ensure that they are performing at optimal levels.
- The ideal test is not the most inexpensive but the most cost-effective.
- The Supranational Reference Laboratory Network has played a key role in determining the extent of drug resistance by conducting representative surveys in broad regions, assessing the quality of TB programs, and informing policy decisions.
- The establishment of national reference laboratories, intermediate reference laboratories, and laboratories in medical colleges, together with plans for dozens more laboratories for liquid plus molecular testing, will increase laboratory capacity.

Successful treatment of MDR TB requires knowing which treatments will work. Today, most diagnoses of MDR TB are made in culture, but this method can take months to produce results, during which time drug-resistant TB patients can continue to infect other people if they are receiving inadequate treatment. Many new diagnostic technologies now being developed are faster and more accurate, but all technologies involve trade-offs between advantages and disadvantages. Four workshop presenters discussed the next generation of TB diagnostics and strengthening of laboratory capacity. Their presentations addressed the advantages and disadvan-

tages of new technologies compared with current methods, the performance testing and quality assurance needed for new technologies, the history and current responsibilities of the Supranational Reference Laboratory Network, and the contributions of FIND and the EXPAND-TB program to the scaling up of laboratory capacity in India.

DIAGNOSIS OF DRUG-RESISTANT TB¹

As discussed earlier, the lack of diagnostic capacity has been a crucial barrier to the treatment of MDR TB. Today, however, at least 20 new diagnostic technologies are in different stages of development, and expanding laboratory capacity has become a global priority.

Ideally, DST should have at least the following characteristics:

- high intra- and interlaboratory reproducibility;
- short turnaround time;
- ability to distinguish between high and low levels of resistance;
- practicality and affordability;
- minimal investment and costs for consumables;
- minimal labor time; and
- applicability to both first- and second-line drugs.

Culture methods, which are regarded as the gold standard, are still widely used today, but have limitations, including

- long turnaround time;
- failure to provide precise identification of species;
- possibility of negative cultures for patients on treatment;
- laborious testing procedures, including standardization of critical concentrations and establishment of appropriate inoculum size; and
- issues concerning the stability of the drug in different culture media, the reliability of results, and quality assurance.

Several rapid assays measure resistance directly from clinical specimens. For example, a meta-analysis showed that the nitrate reductase assay (NRA) has a pooled sensitivity for detection of isoniazid and rifampicin resistance of 94 percent and 96 percent, respectively (Bwanga et al., 2009). The same analysis found a pooled sensitivity for the microscopic observation drug susceptibility (MODS) assay of 92 percent and 96 percent, respec-

¹ This section is based on the presentation of Camilla Rodrigues, Consultant Clinical Microbiologist and Chair of Infection Control, Hinduja Hospital.

tively. This method has the additional benefit of accurate case detection and simultaneous identification of MDR. Finally, thin layer agar (TLA) culture has sensitivity, specificity, and predictive values of 100 percent for isoniazid and rifampicin resistance (Robledo et al., 2008).

Other new methods, such as the mycobacteria growth indicator tube (MGIT), detect metabolic activity or products. With these methods, the time to detection is 10-14 days, compared with 3–4 weeks or more with other methods. Universally accepted standards for critical concentrations are needed to ensure the reproducibility of DST on second-line drugs. One study, for example, found that 21 supranational reference laboratories had different critical concentrations as a result of variations in testing systems and media (Kim et al., 2004). Quality assurance is therefore a critical factor (Rodrigues et al., 2008).

Colorimetric redox indicator (CRI) assays, which are fast and inexpensive, have good sensitivity for isoniazid and rifampicin but do not perform as well for ethambutol and pyrazinamide, said Camilla Rodrigues, Consultant Clinical Microbiologist and Chair of Infection Control, Hinduja Hospital. They also raise concerns about biosafety and containment.

Phage-based technologies were extremely promising when they first appeared; however, that initial promise has faded in recent years. Improved phage technology is currently being developed in the United States and South Africa, and has again raised the hope of this technology being used for both rapid diagnosis and DST. Lysis with mycobacteriophages is fairly sensitive for rifampicin and isoniazid resistance but has limitations in such areas as analytical sensitivity and application to smear-negative patients (Krishnamurthy et al., 2002).

Finally, the detection of specific mutations has advanced through the rapid development of genotypic hardware. This technique has proven most effective with rifampicin but might be less successful with other drugs—for example, isoniazid and the fluoroquinolones, where *M.tb.* has more mutations that code for drug resistance.

Molecular DST includes DNA sequencing, polymerase chain reaction (PCR) single-strand conformational polymorphism (SSCP), solid phase hybridization assays, real-time formats, and microarrays. The advantages of molecular methods are

- rapid provision of results;
- high sensitivity;
- good performance characteristics;
- direct application to clinical specimens;
- less biohazard risk;
- feasibility of automation and high throughput; and
- ability to target genomically based resistance.

However, molecular methods also have limitations:

- polyresistance due to the effects of multiple genes;
- requirements for infrastructure, experienced staff, and funding;
- risk of false-positive tests, especially with methods that target only known or described mutants; and
- silent mutations, or infections with more than one strain.

DNA sequencing is the most informative molecular method, but it is so labor-intensive and expensive that it cannot be used routinely. Other methods are good at detecting specific mutations, but they also can be labor-intensive and somewhat dependent on the person who performs the test. Real-time formats and microarrays are promising but expensive.

Microfluidic technologies may help close the gap between needs and capabilities, especially to the extent that they permit integration of different technologies. For example, GeneXpert MTB/RIF is a self-contained, closed, fully integrated, and automated platform that provides results for detection of rifampicin resistance within 2 hours. The test has a sensitivity almost equal to that of culture, requires minimal hands-on technical time, and can be used in laboratories with considerably less biohazard risk. In a recent study (Boehme et al., 2010), GeneXpert MTB/RIF outperformed smear tests, yielding a relative increase in case detection and accurately ruling out MDR TB. Even in countries with little MDR TB, there is value to using GeneXpert to diagnose TB as it is much more sensitive than microscopy and faster than and as sensitive as culture tests. According to Rodrigues, the only disadvantages are that it is expensive and has a relatively low positive predictive value in areas with low MDR TB prevalence.

According to Rodrigues, the ideal test for TB would have the following features:

- provision of rapid results;
- ability to obtain results directly from the specimen with the sensitivity of culture;
- simultaneous detection of resistance;
- on-demand availability;
- capability for single-patient testing;
- ease of use;
- reproducibility;
- robustness; and
- low cost.

Rodrigues stressed that the TB program in India needs to define priorities; strengthen national laboratory capacity with a tiered network at the

subdistrict, district, regional, and reference laboratory levels; work toward universal access; and leverage molecular methods with culture methods, since no single test can stand alone. Validation, quality assurance, and quality control should be an integral part of the system, said Rodrigues.

Finally, Rodrigues cited two particular clinical challenges. The first is simultaneous infections with different strains, which can lead to conflicting test results. The second is the need to be able to distinguish between immune reconstitution inflammatory syndrome (IRIS) and MDR TB in culture-negative patients undergoing treatment.

QUALITY ASSURANCE CONSIDERATIONS IN THE DEVELOPMENT OF NEW DIAGNOSTICS²

To determine whether a diagnostic test is accurate, observed Thomas Shinnick, Associate Director for Global Laboratory Activities, Division of Tuberculosis Elimination, CDC, its performance must be comparable to that of a gold standard. Molecular tests also must be subject to quality assurance to ensure that their performance is being maintained.

Two key properties of any test are accuracy and precision. Accuracy measures validity, while precision measures reliability or reproducibility. The ideal test is both accurate and precise, so that it yields the right answer every time.

With a standard phase II or phase III diagnostic design, estimation of accuracy involves defining a gold standard; ensuring the quality of the testing; recruiting consecutive patients in whom the test is indicated (that is, in whom disease is suspected); performing the gold standard test on separate groups with and without disease; performing the experimental test on all subjects and classifying them as test positives or test negatives; and developing a 2-by-2 table to calculate sensitivity, specificity, predictive values, likelihood ratios, and diagnostic odds ratios.

With respect to molecular tests for drug resistance, a variety of phenotypic tests can serve as the gold standard, including liquid or solid culture and clinical outcomes. Of course, said Shinnick, these gold standards are in actuality “bronze or silver standards. They all have their own problems, and so we are always going to have to be looking at analyzing discordant or discrepant results to understand our test and how it is performing.”

When discrepant or discordant results occur, several possibilities must be considered. The first is the possibility that errors resulted from mislabeling or laboratory cross-contamination. The possibility of a mixed sample also must be considered. The limit of detection of a molecular test is a fac-

² This section is based on the presentation of Thomas Shinnick, Associate Director for Global Laboratory Activities, Division of Tuberculosis Elimination, CDC.

tor as well. Will a test detect only 10 percent drug-resistant strains when other tests are designed to detect 1 percent drug-resistant strains? To examine these possibilities, a patient sample or isolate can be tested repeatedly, target genes can be resequenced, or the minimal inhibitory concentration can be gauged using liquid or solid media. Clinical outcomes are another way of understanding a test's performance.

Both molecular and conventional tests require quality assurance, emphasized Shinnick. In particular, molecular tests need to be subject to both internal quality controls and external quality assurance. Molecular tests typically involve the use of negative controls, with every test being run to assess the possible contamination of reagents. They also involve the use of positive controls—isolates with particular features used to show that a reagent is behaving as it should. It is important to keep the positive controls away from the test samples to avoid contamination.

External quality assurance ensures that a test is performing the same way in all laboratories. Methods used for external quality assurance include sending an isolate with a known mutation to a laboratory to determine whether the right answer has been obtained; comparing results of another molecular or phenotypic test with the test results; or using laboratory performance indicators, such as the level of agreement among results of molecular or phenotypic tests, the concordance between different samples from the same patient, or the percentage of indeterminate results.

The accuracy of a test determines its value to the clinician. One way of measuring a test's accuracy is by calculating its sensitivity and specificity, which are the rates of the test's true positives and true negatives. For clinicians, the most important pieces of information are the likelihood ratio and diagnostic odds ratio, which are essentially inverses of each other. The likelihood ratio denotes whether the test is more likely to be positive in a diseased than in a nondiseased person. Tests with high likelihood ratios give clinicians more information about how to proceed with treatment.

Shinnick concluded by saying that the ideal test is not the most inexpensive but the most cost-effective. Even a relatively expensive test, such as GeneXpert, can be cost-effective when it rapidly identifies MDR TB patients. The patient is treated sooner and has better outcomes, and the community is protected against the transmission of drug-resistant organisms.

THE SUPRANATIONAL REFERENCE LABORATORY NETWORK³

When the international Supranational Reference Laboratory Network was initiated in 1964, it consisted of 16 laboratories with strong commit-

³ This section is based on the presentation of Nagamiah Selvakumar, Scientist G, National Institute for Research in Tuberculosis.

ments to national TB programs. In general, there was an extreme scarcity of good laboratories at the time.

Initially, 11 of the laboratories were in Europe and 2 in India. The network now includes 2 laboratories in the African region, 5 in the Americas, 1 in the Middle East, 11 in Europe, 5 in the Western Pacific, and 2 in South Asia. One of the latter two is the National Institute for Research in Tuberculosis, Chennai, and the other is in Bangkok.

At the outset, the laboratories periodically collected information on drug resistance in their regions, said Nagamiah Selvakumar, Scientist G, National Institute for Research in Tuberculosis. They had commitments to cover at least two countries other than those in which they were located. They also agreed to ensure the quality of drug resistance surveys by retesting isolates. They participated in annual external quality assessment programs with the coordinating center in Antwerp, Belgium. If possible, they conducted operational research to generate data and provide information to inform policy decisions.

Today the Supranational Reference Laboratory Network determines drug resistance globally through representative surveys in broad regions. It seeks to differentiate between previously treated and untreated cases while continuing to assess the quality of TB programs. It also continues to provide information to inform policy decisions and enhance laboratory capacity.

The network has produced four global reports, the first in 1997 and the most recent in 2008, based on data from an increasing number of laboratories and countries. The network estimates the prevalence of TB, MDR TB, and XDR TB. It also identifies “hot spots” for drug-resistant TB. For example, a recent national survey in China found that 5.7 percent of new TB cases and 26 percent of previously treated cases were MDR. Subnational data from Tajikistan revealed that 16 percent of new cases of TB and 62 percent of previously treated cases were MDR. Overall, based on quality-controlled data from 114 countries, MDR TB occurred in 3.6 percent of incident TB cases in 2008 (WHO, 2010c).⁴

The data also show that 58 countries had reported XDR TB as of March 2010, with approximately 25,000 cases emerging every year. Overall, an estimated 5.4 percent of MDR TB cases are XDR.

Another important function of the Supranational Reference Laboratory Network is to conduct external quality assessments to ensure that the data being generated are reliable. The coordinating laboratory in Antwerp sends a panel of 30 cultures to the supranational reference laboratories every year. The cultures have different combinations of resistance and have been clinically well validated. In recent rounds of testing, 16 of the 27 supranational

⁴ See footnote 4 in Chapter 1 and the updated WHO (2011a) report on TB control for more information on global estimates of MDR TB.

reference laboratories consistently performed better than other laboratories being assessed (Van Deun et al., 2011). The objectives of external quality assessment are to standardize techniques, validate methods, and improve the precision of reporting.

As an example of the activities of a supranational reference laboratory, Selvakumar described those of the National Institute for Research in Tuberculosis, Chennai. It supports not just India, but also Sri Lanka, the Maldives, and, until recently, North Korea (which is now supported by the laboratory in Bangkok). It develops protocols and conducts retesting and panel testing for the external quality assurance program. It also conducts DST for suspected cases of MDR TB. It facilitates international training programs on laboratory diagnosis of MDR TB and quality assurance microscopy. And it participates in WHO meetings and serves as a consultant to other Southeast Asian countries.

In the 16 rounds of quality assurance that have been completed at the National Institute for Research in Tuberculosis, Chennai, efficiency has been acceptable for all first-line drugs except rifampicin, for which results were indiscriminate in two rounds. In the last two rounds, DST has been conducted with second-line drugs, with acceptable efficiency being found for ofloxacin, kanamycin, amikacin, and capreomycin.

The National Institute for Research in Tuberculosis, Chennai, conducted the first statewide drug resistance survey for Gujarat and will be conducting surveys in 2011–2013 for Tamil Nadu and Rajasthan. It monitors India's other national reference laboratories, intermediate reference laboratories, regional medical research centers, and private laboratories.

The Supranational Reference Laboratory Network has made substantial contributions to policy making. The first and second global reports provided information on the MDR TB problem and identified the hot spots in the Soviet Union and China, contributing to the origins of the DOTS-Plus program and the GLC. The third report suggested that previously treated cases and HIV status be included in drug resistance surveys. That report also pointed to the unreliability of second-line DST. This information helped WHO's Global Laboratory Initiative (GLI) formulate guidance for the development of 150 national reference laboratories and almost 8,000 advanced diagnostic centers, and improved the training of hundreds of thousands of microbiologists and technologists.

The National Institute for Research in Tuberculosis, Chennai, also provides information to inform policy decisions. For example, it has recommended having two sputum samples for diagnosis and treating the presence of bacilli in a single smear as an indicator of TB. It also has shown that the sensitivity of diagnoses can be seriously affected when sputum samples are transported in cetyl-pyridinium chloride (CPC) solution, implemented a lot

quality assurance system, and developed software for analysis of retesting and panel testing results.

According to Selvakumar, the Supranational Reference Laboratory Network still has important limitations:

- Not all the high-burden countries have national reference laboratories.
- Many national reference laboratories lack the resources and expertise needed to conduct drug resistance surveys.
- Only the results of panel testing are known, but the results of retesting are needed to ensure the quality of testing.
- External quality testing for the LPA needs to be considered because intermediate resistance to rifampicin has emerged as a problem.
- The role of operational research in national reference laboratories or supranational reference laboratories is not clearly defined.
- Other challenges include inadequate staffing, the threat of contractual staff leaving the laboratory, excessive workloads, and inadequate laboratory infrastructure and staff training.

EXPANDING LABORATORY CAPACITY IN INDIA FOR THE DIAGNOSIS OF DRUG-RESISTANT TB⁵

FIND was created in 2003 to drive the development and implementation of accurate and affordable diagnostic tests that are appropriate to patient care in low-resource settings, said Neeraj Raizada, Medical Officer, FIND. FIND's India office was established in 2007 and had two broad initial projects. One was to conduct an LPA demonstration project and a liquid culture, DST, and rapid speciation laboratory preparedness study. The other was to complete demonstration projects on several new technologies, including light-emitting diode (LED)-based fluorescent microscopy and cartridge-based nucleic acid amplification testing (NAAT). Data from these two projects were presented regularly to the RNTCP and to the DOTS-Plus committee. The data contributed to the RNTCP's laboratory scale-up plan and to the endorsement of the LPA, liquid culture, and rapid speciation tests under the EXPAND-TB and Global Fund projects.

The RNTCP's laboratory scale-up plan called for introducing the LPA in 43 laboratories and liquid culture, DST, and rapid speciation in 33 laboratories (see Chapter 2). The LPA will be the primary diagnostic tool, with follow-up using solid or liquid culture. The turnaround time will be 3 days, compared with the baseline of 4.5 months. Laboratory capacity is expanding to 12,000 LPAs annually, compared with a previous capacity to conduct 5,000 cultures and drug susceptibility tests. The plan is to be

⁵ This section is based on the presentation of Neeraj Raizada, Medical Officer, FIND.

implemented in a phased manner, with the LPA being introduced into 12 laboratories in 2010–2011, 14 laboratories in 2011–2012, and 17 laboratories in 2012–2013. The implementation of the RNTCP laboratory scale-up plan is being funded by various sources.

The EXPAND-TB project was initiated in India in March 2010 with UNITAID and has three implementing partners: FIND, the STOP TB Partnership GLI, and the WHO GDF. A major initiative has been the Global Fund Round 9 project, in which FIND is implementing the laboratory component. The laboratory component complements the EXPAND-TB project in the introduction of rapid diagnostics. Support also comes from the RNTCP and from National Rural Health Mission and state funds.

The specific operational objectives of the EXPAND-TB project are to accelerate and expand access to quality-assured new diagnostics; leverage price reductions for diagnostic tools, instruments, reagents, and supplies; foster a greater number of suppliers of new TB diagnostics, thereby having an impact on market dynamics and achieving a further cost reduction for rapid diagnostics; and improve the case detection and management of TB and MDR TB. The program is supporting the development of a preidentified list of approved equipment and consumables, including LPA and liquid culture equipment. It also is supporting 40 laboratories for LPA equipment and consumables, and 31 laboratories for liquid culture equipment and consumables. The Global Fund Round 9 project further supports these laboratories in the implementation of the national laboratory scale-up plan through human resources, equipment, on-site technical support, and long-term mentoring and provides funds for human resource development and related costs for on-site technical support.

Introducing LPA testing, very broadly, involves five steps:

1. establishing two to three clean rooms, including a hybridization room, an amplification room, and a master mix room;
2. supplying equipment and consumables for LPA;
3. training of both laboratory and field staff;
4. establishing LPA proficiency through a mechanism approved by the National Laboratory Committee; and
5. creating mechanisms for rapid transportation of patient specimens and reporting of results.

According to Raizada, introducing liquid culture is more challenging than introducing the LPA. It involves the establishment of a biosafety level 3 laboratory along with air-handling and cooling units. Training and proficiency testing are necessary. Also, MGIT requires an uninterrupted supply of electricity, which in turn requires power backup at each laboratory because of the erratic power supply in some parts of India.

As of April 2011, 28 districts in India representing a population of 46 million had screened 2,658 suspected cases of MDR TB in the previous year. For these cases, 92 percent of LPA results were available at the time of data collection, and 8 percent of test results were still pending. The invalidity rate in the uncontrolled field setting was 8 percent. Forty percent of samples were diagnosed with drug-resistant TB. The average time between collection of specimen from the field, transportation to the LPA laboratory, and testing and reporting of results was 7 days. Meanwhile, backup testing with Löwenstein-Jensen medium returned results on only 52 percent of the samples.

The strengths of the Indian laboratory scale-up experience thus far have been

- strong coordination at all levels in implementing the drug-resistant TB response plan;
- quarterly national-level meetings by the Central TB Division, with the participation of the national reference laboratories and all implementing partners;
- strong coordinated efforts in human resource development;
- proactive program leadership at the central and state levels;
- fast-track budget mobilization at the state level; and
- contributions of WHO and RNTCP consultants in addressing field problems.

Key challenges have included

- dealing with delays in the development of an online management information system;
- ensuring an uninterrupted supply of second-line drugs;
- maintaining laboratory proficiency despite drug shortages; and
- delivering treatments as volume increases and turnaround times decrease.

POTENTIAL INNOVATIONS AND ACTION ITEMS

Through the presentations provided in this session and the subsequent discussions, individual workshop speakers and presenters noted key innovations and action items. They include the following:

- Priorities for all aspects of the TB program in India are needed, including for diagnosis, laboratory capacity, treatment, and infection control.

- A strengthened tiered network at the subdistrict, district, regional, and reference laboratory levels is essential.
- Because no single test can stand alone, molecular methods should be leveraged with culture methods.
- Fostering a greater number of suppliers of new TB diagnostics would affect market dynamics and achieve a further cost reduction for rapid diagnostics.

6

Addressing TB and Drug-Resistant TB in Vulnerable Populations

Key Messages

- The difficulty of obtaining positive cultures in children complicates the treatment of MDR TB and has obscured the extent of drug resistance in pediatric TB cases.
- Many children are infected by the adults with whom they live, but in a significant fraction of cases, the infection comes from elsewhere.
- In one study from Peru, children living in households with an MDR TB patient had 10 times the risk of infection of the general population.
- Coinfection with HIV and drug-resistant TB is a serious threat to TB control.
- Asia has a history of major refugee movements, and refugee status can lead to displacement and overcrowding, which lead in turn to the spread of infection.

Some vulnerable populations—including children, people coinfecting with HIV, and refugees—are at higher risk of contracting TB and are more difficult to treat than others. Speakers at the workshop addressed each of these three populations, discussing MDR TB among children in India, Peru, and globally; data from India and elsewhere linking HIV infection to drug-resistant TB; the occurrence of drug-resistant TB among Tibetan refugees living in India; and case studies dealing with vulnerable populations (children in Cambodia and MDR TB patients in Ethiopia, many coinfecting with

HIV). All of the speakers emphasized the particular difficulties of reaching vulnerable populations and the steps that must be taken to identify, diagnose, and treat MDR TB among these groups.

DRUG-RESISTANT TB IN PEDIATRIC POPULATIONS¹

A major risk for pediatric TB is contact with an infected adult, observed Soumya Swaminathan, Head, Division of Clinical Research, National Institute for Research in Tuberculosis. Rates of infection among adults aged 25–44 are highest in the African region, followed by Southeast Asia (Figure 6-1), and the risk of TB in children is likely to be correspondingly high in these regions. Other risk factors include large household size, severe malnutrition, exposure to household smoke, having a female index case, and in some cases, being a member of certain minorities.

Like adults, children tend to go through several phases after infection with *M.tb*. After an initial phase marked by hypersensitivity responses and skin test conversion, which typically occur in the first 6–8 weeks, the primary disease follows. Most of the disseminated disease tends to occur in the first 2–4 months after infection. Lymph node disease in younger children and pleural disease in older children can occur at 6–8 months. The adult form of the disease, which generally is seen in older children, can occur several years after infection.

Swaminathan explained that more children than adults with TB are smear-negative, although this varies with the population under study. In one study of 1,098 children seen at the LRS Institute of Tuberculosis and Respiratory Diseases in New Delhi, 414 children were smear-positive, 404 were smear-negative, and sputum status was not known for 280 patients (Sharma et al., 2008). The smear-positivity rate was higher among older children—about 60 percent—but even among children younger than 6 years old, 30 percent were smear-positive.

Unknown Burden of Pediatric MDR TB

Data on MDR TB in children are virtually nonexistent. WHO does not include children in drug resistance surveys, and most countries have not collected these data systematically. A plan to gather data on children is urgently needed, said Swaminathan.

¹ This section is based on the presentation of Soumya Swaminathan, who was Coordinator for Neglected Priorities Research with the WHO Special Programme for Research and Training in Tropical Diseases (TDR) at the time of the workshop. Since the workshop, Swaminathan has rejoined the National Institute for Research in Tuberculosis as Head, Division of Clinical Research.

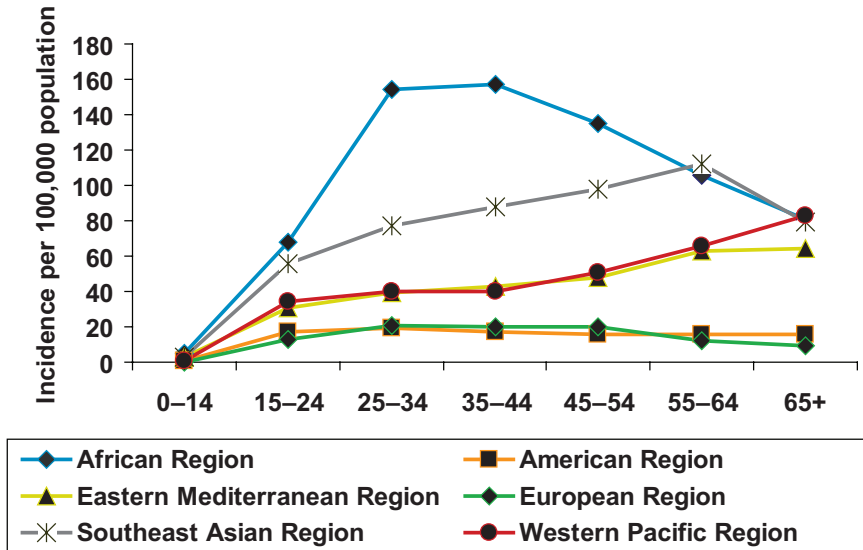


FIGURE 6-1 TB incidence rates are highest in young adults in the African and Southeast Asian regions.

SOURCE: Swaminathan, 2011.

In India, an estimated 7 percent of the reported 1.3 million new TB cases annually are in children. This percentage ranges from 2 percent of new smear-positive cases to 15 percent of new cases of extrapulmonary TB. The percentage of drug-resistant TB is more difficult to estimate. In the Western Cape Province of South Africa, Schaaf and colleagues (2009) found isoniazid resistance to be 7.7 percent among pediatric TB cases and the MDR TB rate to be 6.7 percent, which represented an increase since the 1990s. These levels are higher than in adults in the general TB population in South Africa. Previously treated children had significantly higher rates of drug resistance than new TB cases, and HIV infection was not associated with drug resistance in children, which is also the case in India.

In data from India, MDR TB rates among children with TB were found to be 2 percent about two decades ago (Ramachandran and Prabhakar, 1992).² A few years later, a multicenter study on children with pulmonary TB found a rate of MDR TB of 3.5 percent. These rates depend on the population under study and whether patients are coming from the community or a hospital. In general, said Swaminathan, drug-resistant TB in

² These low pediatric MDR TB rates were observed prior to the implementation of DOTS in India.

children mirrors that in the adult population because adults are the source of their infections.

Challenges in the Diagnosis and Treatment of Pediatric Drug-Resistant TB

Bacterial confirmation of MDR TB in children is not always possible. Instead, drug-resistant TB in a child must be suspected when the child has been in contact with a known case of drug-resistant TB, the child's adult contact has been on chronic irregular treatment and continues to be sputum-positive, the adult contact dies after irregular treatment, or the child shows initial improvement with anti-TB treatment and then deteriorates clinically and radiologically. Contact investigation is vital to detecting pediatric cases of TB and especially MDR TB.

Diagnosis of drug-resistant TB in children requires specimens, such as gastric aspirate, induced sputum, nasopharyngeal aspirate, and extrapulmonary specimens, along with good specimen processing, transport, and testing. The yield of culture in various studies in children has ranged from 10 to 40 percent, depending on patient selection criteria and laboratory methods. The MODS method has been shown to be faster and more sensitive than Löwenstein-Jensen medium. Another study found that MODS has a slightly higher sensitivity than the MGIT method while also being faster (Ha et al., 2009).

GeneXpert has the highest sensitivity in smear-positive culture-positive adults, providing an assessment of rifampicin resistance within about 2 hours, but these data are not available for children. (See the section Case Studies in Cambodia and Ethiopia later in this chapter.) Preliminary data from South Africa show that the sensitivity of GeneXpert is probably around 70-80 percent of culture-positive cases, which represents only 10-40 percent of all pediatric TB cases. More research will be necessary before recommendations can be made regarding the use of GeneXpert with different samples from children.

The treatment approach in children is largely the same as that in adults. Factors to consider include the following:

- The child should receive treatment that is consistent with that of the adult source case if no isolate is obtained from the child.
- At least three or, preferably, four or more drugs to which the isolate is susceptible should be used.
- The child's growth and development need to be monitored, and drug dosages need to be adjusted for weight gain.
- The caregiver needs to receive counseling about adherence, treatment duration, and adverse effects at every visit.

- It has been suggested that early primary pulmonary MDR TB, because of its paucibacillary nature, can be treated for 12–15 months rather than 18–24 months; however, this needs to be validated in clinical trials. Microbiological monitoring is important, but follow-up cultures often are difficult to obtain and more often are negative. Clinical and chest radiographic monitoring during follow-up is helpful.

In one study, the delay in initiating treatment for MDR TB in children was just 2 days if the MDR TB source case was taken into account, but the delay was 246 days if the source case was not considered (Schaaf et al., 2003). The correlation between the DST results for the child and adult was 68 percent in this study, although this correlation can vary greatly from place to place. Obtaining a detailed contact history is essential since a delay in initiating appropriate MDR TB treatment can have serious consequences.

In very small cohorts from Peru, second-line TB treatment was well tolerated by children, even though they had high rates of malnutrition and anemia (Drobac et al., 2006). Even when children showed resistance to as many as five drugs, sputum conversion occurred in a majority of those receiving individualized treatment. However, significant residual sequelae and morbidity occurred, including 24 percent with airway obstruction and 40 percent with restrictive lung disease.

Swaminathan highlighted several challenges in the diagnosis and treatment of MDR TB in children:

- The definition of MDR TB in children is different from that in adults because a culture is not always available.
- Rapid molecular tests need to be studied in the context of pediatric MDR TB.
- More data are needed on the burden of disease in children, including drug resistance.
- More information is needed early in the process of drug development on how new drugs work in children.
- Shorter regimens are needed for MDR TB in children.
- Preventive therapy is needed for MDR TB contacts of children.

THE BURDEN OF PEDIATRIC TB IN HOUSEHOLDS OF PATIENTS WITH MDR TB³

An ongoing study in Peru, presented by Mercedes Becerra, Assistant Professor, Harvard Medical School, is examining the extent of MDR TB

³ This section is based on the presentation by Mercedes Becerra, Assistant Professor, Harvard Medical School.

in the household contacts, including children, of patients with MDR TB. Peru, with a population of almost 30 million, about 10 million of whom live in Lima, recently was removed from the list of the 22 countries with the highest TB burden. It now has an annual TB case notification rate of just over 100 per 100,000 population. Eighty percent of TB cases in the country are found in the capital, and the disease is concentrated in the capital's poorer districts.

In the last national drug resistance survey, which was conducted in 2006, MDR TB was found in 5 percent of new TB patients and in 23 percent of those with a history of TB treatment. HIV coinfection still is relatively rare in MDR TB patients, with an estimated seroprevalence of around 0.5 percent and a rate of about 1.4 percent.

Study Environment and Design

In 1996, Partners In Health, in collaboration with the government of Peru, launched a program to treat patients with confirmed MDR TB, leading to a cure for about two-thirds (Mitnick et al., 2003, 2008). In 2004, the program conducted a retrospective cohort study to determine what had happened to the family members of these MDR TB patients, including children. First, each patient who had started the MDR TB treatment regimen between 1996 and 2002 was identified. A study team visited the households of these index patients and interviewed them and others in the household, asking specifically about TB treatment in any of the household members. The study team then reviewed the medical charts at public health centers of each household member who had reported TB treatment to obtain the dates of the regimen received and other details.

With these data, the study team confirmed the list of individuals who had been living with patients when they started their MDR TB regimen. The team also identified those who had been treated for TB after the index patients started their regimen. In January 2011, the team published a first report about the TB disease burden in this cohort of almost 5,000 household contacts (Becerra et al., 2011).

Study Results and Findings

Unpublished data being prepared for publication as of the time of the workshop cover 1,299 children in the households studied, 70 percent of whom had at least 4 years of follow-up from the time the index patient started the MDR TB regimen. Child household contacts were defined as those less than 15 years of age. Three key results emerged from these data.

First, 67 children in the households were treated for TB disease during this 4-year retrospective observation period, so that pediatric TB accounted

for 20 percent (67/343) of all the TB cases reported in the household contacts. Thus, by the end of this period, more than 5 percent (67/1,299) of the children in the households had been treated for active disease. Furthermore, because 30 percent of the children had less than 4 years of follow-up, this proportion may be an underestimate.

Second, of the 67 children treated for TB, only 8 had DST results in their medical chart, because in children it is difficult to obtain adequate sputum specimens for testing. Of these eight children, seven had MDR TB isolates. Six of the eight had TB isolates available for genotyping, and all six were found to be an identical genotypic match to the isolate from the index patient. They were most likely either infected directly by the patient or part of the same chain of transmission, so that both were infected by some other source patient. This result strongly suggests that the great majority of the observed TB disease in these children was due to MDR TB transmitted from the index case.

Third, among this population of child contacts, the window to estimate the prevalence of treated TB was defined as the period up to 6 months before and up to 1 month after the date that the index patient started the MDR TB treatment regimen. The prevalence of treated TB was almost 1,800 per 100,000 children. This prevalence was highest among 1- and 2-year-olds—more than 2,500 cases per 100,000 children, which is 10 times the prevalence in the general population. The TB prevalence in 1- and 2-year-olds was similar to that observed in the group of adults. Similarly, the incidence rate of treated TB in all children during the first year of follow-up exceeded 2,200 per 100,000 child-years.

“These disease rates are certainly alarming and should rightly give us pause,” said Becerra. “These rates among children [in the prevalence window and in year 1 of follow-up] are squarely in the range of the TB case rates that were observed in the jails and prisons of Russia in the 1990s.”

The only optimistic finding is that the high-risk window is within the 2-year period that is required to complete an MDR TB treatment regimen. If a patient is being visited by a health worker or treatment supporter during that period, that individual, with enough training and support, can observe others in the household. But programs need clear guidance about how to evaluate the household contacts efficiently over time.

The results of this study are an important reminder, according to Becerra, that the household contacts of MDR TB patients, including children, are a likely source of more MDR TB cases. Children who are living with a patient starting MDR TB treatment are at high risk for having TB. In this study, the estimated prevalence of TB disease at baseline was about 2 percent, which means that at least 50 children would need to be screened to find each TB case. This amounts to roughly 10 times the TB case rates reported in the general population.

Finally, the results underline the need for appropriate pediatric treatment regimens: in the small number of children for whom DST results were available, as in the larger number of adults tested, approximately 90 percent had MDR TB. To optimize their chance of being cured, children with MDR TB require regimens designed to treat drug-resistant disease.

During the discussion period, Edward Nardell, Harvard Medical School, noted that inhaled drugs, particularly kanamycin and capreomycin, could offer promise in the treatment of children. Preliminary studies in guinea pigs reveal that inhaled capreomycin can achieve therapeutic levels in the blood and high levels in the lung (see, for example, Fiegel et al., 2008; Garcia-Contreras, 2007). Although very young children might have difficulty with inhalation, many children already receive asthma medication by that route.

Becerra noted the possibility of using a shorter treatment regimen with children because their disease is being detected in an earlier phase relative to adults. Nardell also cited the possibility of treatment with experimental drugs because the drugs could be used under controlled circumstances to look for an effect in a very short time.

There was some discussion about the use of prophylactic therapy in contacts of TB and MDR TB patients. One participant asked whether children should be considered a high-risk population and be offered DST even if they are not smear-positive, despite limited laboratory resources. Salmaan Keshavjee, Harvard Medical School, responded that this practice would represent a major policy change in the developing world, although it is seen in the developed world.

DRUG RESISTANCE IN HIV-INFECTED POPULATIONS⁴

Coinfection with HIV and drug-resistant TB is a serious threat to TB control, said Digambar Behera, Director, LRS Institute of Tuberculosis and Respiratory Diseases. Kawai and colleagues (2006) found that more than 50 percent of HIV-MDR TB patients in Peru died within 2 months of diagnosis. Studies with longer follow-up observed death rates ranging from 72 to 89 percent (Coker, 2004). Authors of a study in the United Kingdom estimated that MDR TB patients who are immunocompromised are nine times more likely to die than those who are not immunocompromised (Drobniewski et al., 2002). In a 2005–2006 study in the province of KwaZulu-Natal, South Africa, 98 percent (52 of 53) of coinfecting XDR TB and HIV patients died, with a median survival time of 16 days from the XDR TB diagnosis (Gandhi et al., 2006). A follow-up, retrospective,

⁴ This section is based on the presentation of Digambar Behera, Director, LRS Institute of Tuberculosis and Respiratory Diseases.

observational study in South Africa conducted from 2005 to 2007 revealed that while 1-year mortality for MDR and XDR TB patients had improved, the majority of deaths—40 percent of MDR TB cases and 51 percent of XDR TB cases—still occurred in the first 30 days after diagnosis (Gandhi et al., 2010). Among the 272 diagnosed MDR TB patients and 382 XDR TB patients in this study, HIV coinfection rates were 90 and 98 percent, respectively (Gandhi et al., 2010).

Although HIV infection has been associated with MDR TB outbreaks in institutional settings, such as hospitals and prisons, whether HIV infection also is associated with MDR TB outbreaks in community settings remains unclear. In Thailand, data collected prospectively on pulmonary TB cases treated in public clinics showed that HIV is common among MDR TB patients but is not an independent risk factor for MDR TB (Akksilp et al., 2009). Nevertheless, populations at high risk for HIV—including young adults, men, and injection drug users—should be a priority for DST, said Behera.

A systematic meta-analysis summarizing the evidence from 32 studies found no clear association between MDR TB and HIV infection across time and geographic location (Suchindran et al., 2009). Comparisons of MDR TB prevalence to HIV status ranged from 0.21 to 41.45. Assessment by geographic region or study period did not reveal noticeable patterns. The summary prevalence ratios for acquired and primary MDR TB were 1.17 and 2.72, respectively. While this meta-analysis could not demonstrate an overall association between MDR TB and HIV or acquired MDR TB and HIV, it does suggest that HIV infection is associated with primary MDR TB. In general, well-designed studies and surveillance in all regions of the world are needed to better clarify the relationship between HIV and MDR TB.

Specifically with respect to India, Deivanayagam and colleagues (2002) found that about 60 percent of 1,000 TB patients were culture-positive, and 34 percent had MDR TB. The HIV seropositivity in the MDR TB group was around 4.4 percent. Swaminathan and colleagues (2005) found that the MDR TB rate in both new and previously treated TB cases was not substantially different in HIV-positive and HIV-negative patients. However, a study from Pune (Pereira et al., 2005) found that 10 percent of HIV-positive patients and only 2.5 percent of HIV-negative patients had MDR TB. S. Singh and colleagues (2007) determined that of 54 patients with AIDS, 12 were resistant to first-line drugs, and 4 of these were also resistant to second-line drugs.

Reports of XDR TB in India have been surfacing. However, most of these reports do not include information about HIV status (Table 6-1).

With a population of about 1.21 billion, India has about 480 million people infected with TB (Figure 6-2). It also has an estimated 2.27 million people infected with HIV. People coinfecting with TB and HIV are estimated

to number around 1 million. Of the approximately 2 million new TB cases annually, an estimated 100,000 will have both HIV and TB infection, given that about 5 percent of incident TB cases are estimated to be HIV-positive (Dewan et al., 2010). However, the TB epidemic in India is being driven primarily by the 400 million people with TB who are not coinfecting with HIV.

The proportion of registered TB patients who are HIV-positive is highly variable, ranging from less than 1 percent to more than 10 percent in different parts of India. Within some districts, as many as 46 percent of registered TB patients are HIV-positive.

Overall, said Behera, studies in India have not demonstrated an association between HIV infection and MDR TB, a finding that contrasts with results of studies conducted elsewhere. However, the National Laboratory Committee has decided that all future drug resistance surveys should capture HIV status and that TB patients should routinely be referred for HIV testing.

Great challenges remain in the areas of diagnosis and treatment of TB-HIV coinfection, said Behera. For example, DOTS-Plus does not include a separate program for HIV-positive patients, and drug interactions in coinfecting patients can be difficult to manage. However, a TB-HIV collaboration begun in 2001 is conducting joint training, intensified case finding, and HIV testing of TB patients with HIV risk factors. It has scaled up its activities to 14 states and has piloted routine referral of TB patients for HIV testing. A phased expansion of the TB-HIV initiative will cover the entire country by 2012. Operational guidelines for airborne infection control, refinement of treatment, and development of training materials all are under way.

DRUG-RESISTANT TB IN MIGRANT AND REFUGEE POPULATIONS⁵

The United Nations (UN) High Commissioner for Refugees defines a refugee as a “person who owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion, is outside the country of his nationality and is unable to or, owing to such fear, is unwilling to avail himself of the protection of that country.” An internally displaced person is a person sharing the characteristics of refugees but displaced within the boundaries of a country. The UN estimates that in 2006 there were more than 32 million refugees, internally displaced people, or similarly vulnerable people.

Asia has a history of major refugee movements. Since 1979, nearly

⁵ This section is based on the presentation of Kunchok Dorjee, Director, Tibetan TB Control Programme, Delek Hospital.

TABLE 6-1 Profile of XDR TB in India

Study	Setting	No. of MDR TB Cases	No. of HIV-Positive Cases	Prevalence of XDR TB (%)	Reference
Mondal and Jain, 2007	Tertiary care center, Lucknow	68	Not reported	5 (7.4)	<i>Emerging Infectious Diseases</i> , 2007
Singh et al., 2007	Tertiary care center, New Delhi	12	All HIV-infected	4 (33.3)	<i>AIDS</i> , 2007
Sharma et al., 2009	AIIMS, New Delhi, tertiary care hospital	211	All HIV-negative	5 (2.4)	<i>Indian Journal of Medical Research</i> , 2009
Ramachandran et al., 2009	Gujarat, field study	216	Not reported	7 (3.1) (all previously treated cases)	<i>International Journal of Tuberculosis and Lung Disease</i> , 2009
Myncedu et al., 2011	LRS Institute	223	Not reported	45 (20.17)	<i>International Journal of Tuberculosis and Lung Disease</i> , 2011

SOURCE: Behera, 2011.

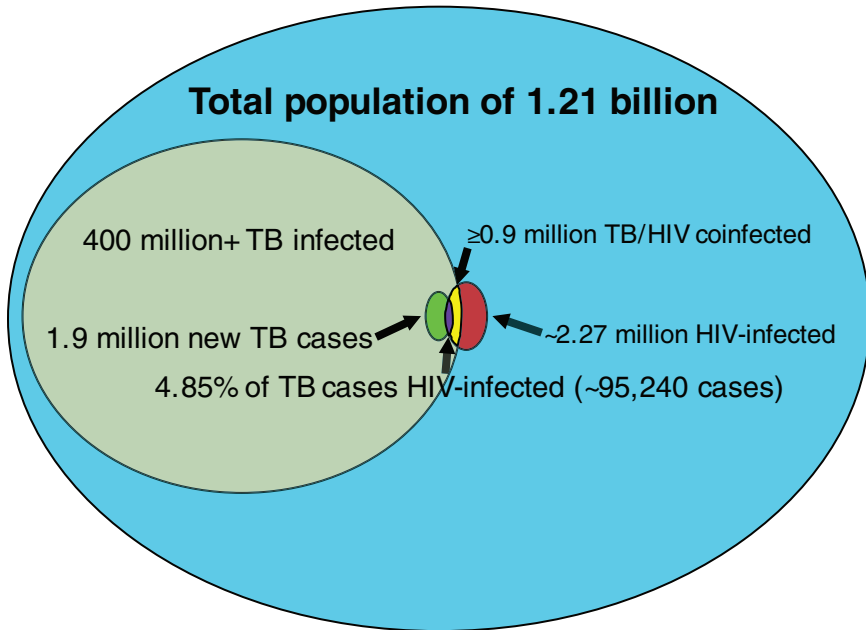


FIGURE 6-2 The TB epidemic in India is being driven primarily by the approximately 400 million people infected with TB who are not coinfecting with HIV.
SOURCE: Behera, 2011.

6 million Afghan refugees have moved in and out of Pakistan and Iran. The 1947 partition of India and Pakistan created the largest movement of people in history—15 million. And in 1959, when the Himalayan refugee crisis occurred, thousands of Tibetan refugees fled into India, Nepal, and Bhutan.

Refugee status is a driver of TB, said Kunchok Dorjee, Director, Tibetan TB Control Programme, Delek Hospital, because it results in displacement, a scarcity of shelter, and overcrowding, which in turn lead to the spread of infections, including TB. Refugee status also can lead to delayed diagnosis as a result of such factors as financial and personal hardships, reluctance to visit a doctor for anything less than an urgent condition, language and cultural barriers, and a lack of health education. Delayed diagnosis of TB can in turn lead to increased spread in the community. These same factors can result in poor treatment adherence, default, and the emergence of drug-resistant strains.

In 1959, thousands of Tibetans followed the Dalai Lama into exile. The government of India provides asylum to Tibetans who continue to flee

across the Himalayas into exile in India. Tibetans have resettled in various locations throughout India. The Tibetan Government in Exile is seated at Dharamshala, Himachal Pradesh.

In the early years of exile, a large number of Tibetans died from TB. The Department of Health of the Tibetan Government in Exile estimates that the TB prevalence at that time was 30 percent of the entire exiled population, although the exact number is not known.

The total population of Tibetan refugees is about 150,000, with the largest number residing in India. It is an extremely mobile population, with people coming into India and returning to Tibet annually. People move across the Indian, Nepalese, and Tibetan borders and within countries, which makes individual case management challenging. Many Tibetans live in closed and congregate settings, such as dormitories in schools, monasteries, nunneries, and reception centers for newly arrived refugees. This situation makes community transmission very easy and delayed diagnosis very costly, said Dorjee.

In the 1990s, the incidence of TB among Tibetan refugees in India was about 835 per 100,000 population (Nelson et al., 2005). A study of Tibetan immigrants from India and Nepal to Minnesota showed a positive tuberculin skin test (TST) rate of almost 98 percent (Truong et al., 1997). Among Tibetan refugee claimants in Toronto, almost 97 percent were TST-positive (Marras et al., 2003).

The number of new TB cases detected in the Tibetan population in South India was relatively stable from 2006 to 2010, ranging from 223 to 291. Of these, between 14 and 23 were MDR TB cases, with a surge of cases, from 9 to 23, occurring in 2010. One reason for the surge may be that sputum cultures were done in 2010 for every smear-positive and relapsed case, leading to the detection of more MDR TB patients.

At the Tibetan Delek Hospital in Dharamshala, the number of TB cases declined from 290 in 2007 to 171 in 2010. But the number of MDR TB patients stayed roughly stable, ranging between 33 and 43. Many of the MDR TB patients at the hospital are college students, who must withdraw from school to take their treatment for 2 years. These patients also include monks, nuns, businessmen, and the unemployed. Tibetans born in Tibet tend to have fewer cases of MDR TB than of drug-sensitive TB, even though acquired drug resistance is relatively high in Tibet, while Tibetans born in India have more. The number of women with MDR TB is slightly higher than the number of men, and the great majority are between 14 and 40 years old. Resistance to second-line drugs is variable, and some XDR TB strains are beginning to emerge in the Tibetan community.

The size of the Tibetan population is only 6 million, so an epidemic of MDR and XDR TB in the community could be disastrous. Given Tibetans' highly charged political situation, nonpolitical issues such as health care

tend to be overlooked. “MDR and XDR are a risk to the entire generation,” said Dorjee.

CASE STUDIES IN CAMBODIA AND ETHIOPIA⁶

Projects carried out by the Global Health Committee/Cambodian Health Committee, which began working in Cambodia in 1994 and has cured approximately 25,000 people since then, illustrate some of the difficulties of diagnosing and treating vulnerable populations.

Novel Diagnostic Modalities Among Children in Cambodia

The Global Health Committee/Cambodian Health Committee has been investigating novel approaches for TB diagnosis among children in Cambodia. As noted previously, diagnosis of TB in children is challenging. It is often difficult to obtain sputum specimens, and children frequently have paucibacillary disease, which makes microbiological diagnosis uncommon. With standard diagnostic criteria, diagnostic accuracy in children is poor.

At the same time, validation of novel diagnostic technologies is performed primarily among adults. Data on pediatric prevalence and incidence are limited for both TB and drug-resistant TB. No TB drug trials in children are under way, and few pharmacokinetic studies have been conducted in pediatric populations. The result is that little information is available about the efficacy of control and prevention measures.

The project in Cambodia (a partnership between the Global Health Committee/Cambodian Health Committee and the Aeras Global TB Foundation, with funding from the Annenberg Foundation), which was described by Anne Goldfeld, Cofounder, Global Health Committee/Cambodian Health Committee, and Professor of Medicine, Harvard Medical School, is designed to evaluate the performance of GeneXpert and the urine lipoarabinomannan (LAM) assay in a pediatric cohort, evaluate the diagnostic utility of stool specimens, and determine the prevalence of TB disease and latent TB infection in a cohort of Cambodian children. The study involves a cross-sectional survey in a province of eastern Cambodia abutting Vietnam where the Global Health Committee/Cambodian Health Committee has worked since 1994. The study enrolled household contacts of index patients with TB, children attending 28 outpatient health centers, and children admitted to 2 district hospitals, with enrollment being conducted from July 2010 to February 2011.

⁶ This section is based on the presentation of Anne Goldfeld, Cofounder, Global Health Committee/Cambodian Health Committee, and Professor of Medicine, Harvard Medical School.

Children were admitted to Svay Rieng District Hospital, where standardized and systematic TB screening data were collected, including medical history, physical examination, chest x-ray, symptom screening, TB exposure, HIV status, and HIV exposure. The laboratory workup included two gastric aspirates, one induced sputum sample, a stool specimen, and a urine specimen. The microbiological workup included acid-fast direct smear microscopy, Löwenstein-Jensen and MGIT culture, GeneXpert, and urine LAM. Among 876 children enrolled, the TB prevalence was 16 percent. But the yield of microbiological confirmation using routine culture methods in a well-established laboratory at the Institute of Cambodia in Phnom Penh was low—just 1 percent. The TB in these children was being detected very early, which probably increased the rate of overdiagnosis.

GeneXpert could be used for gastric aspirates and provided rapid diagnosis of TB, but it yielded no incremental results compared with the culture method. The results were obtained in 2 hours as opposed to weeks or months, said Goldfeld, but the results demonstrate that other approaches to diagnosing children with TB are needed.

During the discussion period, a workshop participant pointed out that the advantage of GeneXpert and other diagnostic technologies is not necessarily greater sensitivity but the decentralization of analysis. A major difficulty with diagnosis is collecting quality specimens and transporting them to a laboratory, and this difficulty is even greater with children and other high-risk groups. Automated technologies can decentralize diagnosis to such populations, the participant pointed out.

Filling the MDR TB Treatment Gap in Ethiopia

Ethiopia has the world's fifteenth highest burden of MDR TB and is one of the poorest countries in the world. In 2009, the Global Health Committee/Cambodian Health Committee, working under the name Global Health Committee in Ethiopia, initiated the countrywide MDR TB treatment program in partnership with the Jolie-Pitt Foundation and the Ethiopian Ministry of Health.

Among a population of 80 million people, an estimated 130,000 new TB cases occur each year in Ethiopia, including about 6,000 new MDR TB cases, and these numbers are likely to be underestimates, said Goldfeld. Before 2009, a major effort to build laboratory capacity, with assistance from FIND, resulted in 221 MDR TB cases being documented by DST. In August 2008, these 221 patients were waiting in the Addis Ababa area for treatment. A GLC application initiated in 2007 had been approved for the first 45 courses of treatment starting in October 2008.

The Global Health Committee/Cambodian Health Committee brought a team to St. Peter's Hospital in Addis Ababa to help initiate the Ethiopian

MDR TB program. It also brought the Ethiopian MDR TB team to Cambodia to provide didactic and hands-on treatment. As of December 2008, however, there still were no anti-MDR TB drugs in Ethiopia. Furthermore, many other problems challenged the delivery of MDR TB treatment. Isolation beds were not available, and the construction of a new ward at the hospital had been delayed. Human resources were limited, and only partial laboratory testing was available. A pharmacy for second-line drugs had not been established, and an outpatient system did not exist.

Using a supply of capreomycin donated by Eli Lilly & Co. and funding from the Jolie-Pitt Foundation, the Global Health Committee/Cambodian Health Committee initiated MDR TB care, in partnership with the Ethiopian Ministry of Health, at St. Peter's hospital in February 2009. Between then and the arrival of the GLC drugs in September 2009, three cohorts totaling 37 patients began treatment. When the 45 courses of treatment arrived, the treatment team was already assembled, and other issues, such as ancillary medications for side effects and management issues, were under control. By the time the new MDR TB ward at the hospital was completed in June 2010, five more cohorts of patients were receiving treatment. After reviewing the project, the GLC sent another 245 treatment courses to Ethiopia. Another program in Gondar, in northern Ethiopia, began with three patients in August 2010.

As of the time of the workshop, 213 patients had been initiated on therapy, including 183 in Addis Ababa and 17 in Gondar. Seven patients had completed treatment. Eighteen had died, six within the first 30 days, an indication of how sick this group of people was. One of the deceased was a suspected XDR TB case. A total of 188 patients were currently on active treatment as of the workshop—125 outpatients and 46 inpatients in Addis Ababa and 17 in Gondar. Three patients who were presumed to have XDR TB were being treated for it. Only one patient had interrupted treatment.

Of the 221 backlogged cases of MDR TB confirmed by DST, 66 had started on therapy. Twenty percent of these cases were confirmed dead in a house-to-house search, and 50 percent, many of whom presumably had died, could not be located.

Of the 18 deaths among the 213 people treated, the mean time to death was 79 days, with a range of 1 to 298 days. The mean age was 31.5, with a range of 20 to 58. The mean number of prior treatments was 2.24. Comorbidities included severe malnutrition (44.4 percent), HIV infection (33.3 percent), diabetes (16.7 percent), cor pulmonale (16.7 percent), and cirrhosis (5.5 percent). Most people died as a result of respiratory decompensation associated with end-stage TB, including two with probable tension pneumothorax. One had TB pericarditis, another had worsening chest x-rays, another died suddenly with cor pulmonale, and others had probable superimposed pneumonias. At the time the six patients who had been

on therapy longer than 6 months died, three had culture-converted, and three were persistently positive. None of the deaths was the direct result of adverse events attributable to MDR TB.

Among all the patients, the mean age was 30.17 (with a range of 8 to 76). The mean number of prior treatments was 2.65, with a range of 1 to 8, and the HIV coinfection rate was 23 percent. The mean time to culture conversion was 38 days.

The very low default rate has been achieved by engaging family and other social resources in supporting the patient, said Goldfeld. All patients are visited at least once a month in their homes and once a month in the clinic. If their discharge orders include daily injections, they are seen every day in the health center. Health care providers make sure patients are taking their medications and deliver medications to patients who cannot obtain them. Patients sign a contract stating that they will complete treatment. Providers also bring food baskets to patients to support them and help them deal with the gastrointestinal difficulties associated with MDR TB treatment.

The direct collaboration that has been achieved among Ethiopian and Cambodian physicians has been described as a “south-to-south transfer,” or the sharing of expertise and best practices from one resource-limited setting to another. Goldfeld explained that the approach of integrating hospital- and community-based treatment has filled the gap in Ethiopia and provides a model for expansion. A key challenge is to forecast the need for drugs and make them available. Goldfeld contrasted the difficulties faced in obtaining needed drugs with the speed and efficiency of retail systems, noting that “we can get flowers from Holland to Winnipeg in 12 hours. Why can’t we get life-saving drugs from drug stocks controlled by the GDF to countries where patients are dying due to their lack in a timely fashion?” Funds also are needed for clinical care, ancillary medications, basic laboratory tests, staff support, food, and outpatient monitoring. In Ethiopia, these funds come from private sources, which Goldfeld said is surprising since the government sets funds aside for treatment. However, in Ethiopia, it has not been possible to directly access U.S. Agency for International Development (USAID) funds to support treatment of MDR TB, as the substantial funds allocated are directed to historical USAID partners not doing direct care. Similarly, in Cambodia, the initiation and expansion of MDR TB care in the country done by the Global Health Committee/Cambodian Health Committee has been supported by a private donation from the Annenberg Foundation and not by the USAID grants awarded to that country.

POTENTIAL INNOVATIONS AND ACTION ITEMS

Through the presentations provided in this session and the subsequent discussions, individual workshop speakers and participants noted key innovations and action items. They include the following:

- More research to obtain more data on children with MDR TB is urgently needed. Such data could assist those attempting to develop better diagnostics and treatment regimes for children.
- Expansion of ongoing efforts to address the challenges associated with diagnosis and treatment of TB-HIV coinfecting patients is key to controlling the spread of MDR TB.
- “South-to-south transfer,” or the sharing of expertise and best practices from one resource-limited setting to another, offers an opportunity to learn from relevant experiences elsewhere in the world.

Finally, since the workshop, a research network on pediatric drug-resistant TB, The Sentinel Project on Pediatric Drug-Resistant TB, has been launched by two workshop participants.⁷

⁷ Since the workshop, Mercedes Becerra, Assistant Professor, Harvard Medical School, and Soumya Swaminathan, Head, Division of Clinical Research, National Institute for Research in Tuberculosis, collaborated to launch a research network on pediatric drug-resistant TB. As of April 2012, more than 140 individuals from more than 30 countries had come together to collaborate on joint projects through the network, titled The Sentinel Project on Pediatric Drug-Resistant Tuberculosis. More information is available at <http://sentinel-project.org/> (accessed April 30, 2012).

7

Combating Drug-Resistant TB Through Public–Private Collaboration and Innovative Approaches

Key Messages

- The majority of people seeking health care in India, including TB patients, use private providers, highlighting the importance of public–private collaboration in reaching drug-resistant TB patients.
- Cell phones, GPS, electronic medical records, and other technology applications can help ensure that MDR TB patients are being treated effectively and can help engage the private sector in identifying people with drug-resistant TB.
- TB and MDR TB programs that include culturally sensitive integration into poor communities can increase treatment success rates for TB and MDR TB and reduce the stigma associated with the disease.

Many pieces must come together to treat drug-resistant TB effectively in India. The majority of the Indian people receive their health care from private providers, who need to be integrated into systems of TB detection and treatment. Special outreach to poor and isolated communities is needed to reach patients who are struggling to support themselves and their families. The health care system must address the importance of finding and treating MDR TB patients. Several presenters at the workshop addressed these issues, speaking about Operation ASHA's efforts to provide TB treatment to the many poor and underserved patients in India's slums; ways to engage private-sector providers in broad public campaigns to reduce rates

of drug-resistant TB; and innovative ways of using cell phones, electronic medical records, and biometric devices to monitor interactions with TB patients and provide incentives for private health care providers to find and treat these patients.

OPERATION ASHA: “GOING THE LAST MILE”¹

Significant social stigma is attached to MDR TB, said Shelly Batra, President and Cofounder, Operation ASHA. It can cause the loss of a job, the loss of a home or family life, or the denial of education to children. In contrast with many other communicable diseases, MDR TB can be contracted just by being in the same room as a patient, and there is general awareness of this fact. Because of the stigma, many patients experience denial or hide their disease. Many patients also refuse to come forward for treatment, or if they do initiate treatment, they default. Because MDR TB treatment takes 2 years and requires continual management, keeping people in the system is a very big challenge, said Batra.

Many people in India with MDR TB live in the slums and are highly mobile, returning to villages for events such as marriages or deaths. Moreover, DOTS centers often are highly inaccessible. Many are open only during usual business hours—10:00 AM to 5:00 PM. If patients need to choose between food for their family and TB treatment, they will choose food. Some will go for treatment only until they are well enough to work.

The poor in India and elsewhere in the developing world live in absolute poverty, noted Batra, defined by the World Bank as earning less than \$1 a day. The round-trip fare to the DOTS center and back is 20 rupees. A man accompanied by an elderly mother or a baby, then, must pay 40 rupees, which is 80 percent of the day’s wages; therefore, if a man goes for TB treatment, there will be no wages for the day.

Thus, said Batra, TB is not only a disease but also a socioeconomic crisis. In India, TB results in \$300 million in lost wages every year (RNTCP Status Report, 2007). The indirect cost of TB to the Indian economy from lost productivity and absenteeism is \$3 billion a year. Nearly one-third of 11,000 business leaders around the world expect TB to affect their business in the next 5 years, and 1 in 10 expect the effects to be serious (World Economic Forum, 2008). In the words of Jackson and colleagues (2006), “Ongoing poverty reduction programs must also include reducing TB.”

Operation ASHA has engaged in mobilizing the whole community to deliver MDR TB treatment, working in close coordination with the government of India and following RNTCP guidelines. Its focus is on the “last

¹ This section is based on the presentation of Shelly Batra, President and Cofounder, Operation ASHA.

The DOTS model: Network of three types of facilities

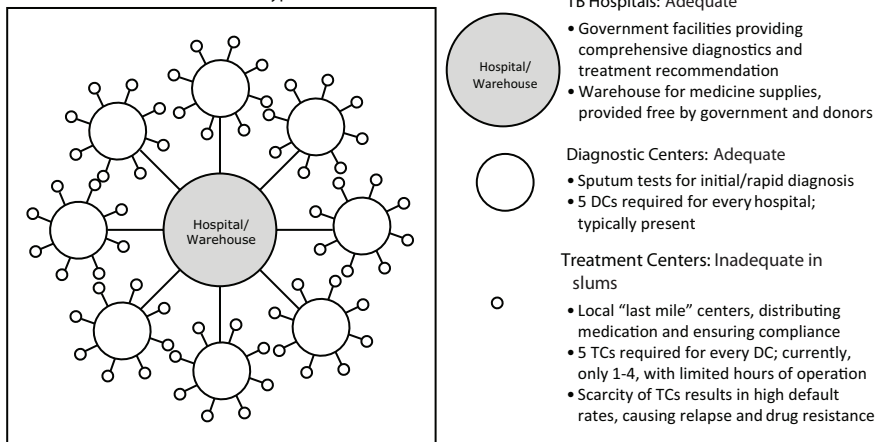


FIGURE 7-1 The DOTS model in India includes a network of three types of facilities: TB hospitals, diagnostic centers, and treatment centers. The government model breaks down in the "last mile," where treatment centers are located in the slums. NOTE: DC, diagnostic center; TC, treatment center. SOURCE: Batra, 2011.

mile" to the slums, beyond TB hospitals and diagnostic centers (Figure 7-1). It has created a dense network of treatment centers for MDR TB near the entry point to the slums, at major bus stops, and near factories so that patients are no more than a 10-minute walk from the nearest center. These centers are in shops, temples, and social or religious organizations and are open for extended hours based on community needs, so that people can come before first prayer at a temple at 6:30 AM or after last prayer at 9:00 PM.

The Operation ASHA centers leverage trusted community leaders such as priests and traditional healers to spread key messages to their community. At the same time, privacy is maintained. Treatment can be provided discreetly within a community-based model.

Operation ASHA conducts rapid-response testing and education of the family members and neighbors of identified patients. It also performs active case finding in the community, which has resulted in much higher detection rates of sputum-positive cases.

The project uses a corps of highly trained, well-compensated, full-time counselors to ensure compliance. If a patient misses a dose, a counselor goes to the patient's home to bring him or her back into the system. The counselors receive a cash incentive for tracking missed doses and adminis-

tering them to the patient. The counselors also are responsible for linking patients with hospitals, taking them for sputum testing, and getting boxes of medicine allotted.

Operation ASHA is undergoing an aggressive expansion to enroll 40,000 patients by 2014, up from 5,000 in 2010 and 10,000 in 2011. At that point, the population base served exclusively by the project will number 28 million, and the total population in the areas served will be 80 million.

Operation ASHA's cost for treating drug-susceptible TB is only \$30 per patient, because the government provides the medicine and funds facilities. Of that \$30, 85 percent goes to the core components of the program. Furthermore, beyond free medicines, diagnostics, and physician services, the government of India awards grants per patient 2 years after the completion of treatment, so each center can become self-sustaining after 2 years.

For an MDR TB patient, the estimated cost of diagnostic tests, physician services, and medicines is \$2,340, according to Batra. Beyond those funds and resources invested by the government, Operation ASHA invests an additional \$400 for counselors, administrative costs, and miscellaneous costs, for a total of \$2,740. Batra explained that this is an extremely cost-effective investment, when the reduced health care and other costs to the economy and increased productivity for a patient who has been successfully treated are factored in. However, it can be difficult for Operation ASHA to secure \$400 to treat an MDR TB patient, as opposed to \$30 to treat a drug-susceptible patient.

Operation ASHA started treating MDR TB patients in March 2009 in collaboration with the RNTCP. As of the date of the workshop, 17 patients had been enrolled, 2 of whom had completed treatment in March 2011. The challenges of treating MDR TB patients include difficulties with adherence given the long duration of therapy, intensive counseling, frequent blood and sputum tests, and daily injections for 6 months. The project has found that intensive counseling, combined with a patient-friendly approach, works best, said Batra.

Batra observed that eliminating TB by 2050 will require a rate of decline of 16 percent each year, but the current rate of decline is only 1 percent. The involvement of governments, NGOs, the private sector, and communities will be essential to meet the challenge. Aggressive cost containment requires the innovative use of technology; the use of low-cost, high-impact community-driven models; and public-private partnerships to deliver MDR TB treatment, said Batra. The government must encourage NGOs to deliver treatment, especially in challenging and difficult-to-reach areas such as urban slums, villages, and mountainous areas. For their part, NGOs must provide transparency and accountability, Batra stressed.

ENGAGING THE PRIVATE SECTOR IN INDIA²

The private sector dominates health care in India, observed Puneet Dewan, Medical Officer, WHO Regional Office for Southeast Asia. In most parts of the country, the public sector is a minority provider of routine health care. Ambulatory care, human resources, and inpatient care all are dominated by the private sector, and TB care is no different. Two-thirds of India's households rely on private-sector sources for health care (IIPS and Macro International, 2007). Even households in the lowest quintile of wealth use private caregivers 60 percent of the time when members are sick (IIPS and Macro International, 2007). A recent community-based survey of 30 districts in India found that nearly half of patients currently being treated for TB were receiving treatment outside DOTS/RNTCP sources and were not included in the national TB notification system (Satyanarayana et al., 2011). Of 6,771 TB patients included in the 2004 National Sample Survey, 53 percent of outpatients and 43 percent of inpatients reported the use of private health care facilities (Hazarika, 2011). There were no significant differences by age, urban versus rural residence, or education level. The most common reason cited for relying on private care was dissatisfaction with public care, including long waiting times—not lack of access to public services.

Opportunities to Improve Case Finding in Collaboration with Private Providers

According to modeling done by Dye and Williams (2010), reducing treatment delays would have a greater effect on levels of new smear-positive TB cases than would improvements in treatment. Transmission is not driven by the lack of successful treatment of those who are identified as having the disease. Rather, transmission is driven by people in whom TB is not identified or who have not begun receiving the right treatment early enough. According to a recent set of surveys in Southeast Asia, for example, fewer than half of people who were bacteriologically active for TB were smear-positive in Cambodia, Vietnam, and Myanmar. Earlier case finding is particularly critical with MDR TB, said Dewan. If earlier case finding is linked with high-quality and rapid DST, diagnosis can occur earlier in the course of disease, and the subset of patients with drug-resistant TB can be started on the appropriate treatment sooner, reducing their opportunities for transmission.

Tools that shorten the time to diagnosis can have a major effect on

² This section is based on the presentation of Puneet Dewan, Medical Officer, WHO Regional Office for Southeast Asia.

incidence. Decentralizing diagnosis also can have an impact on transmission and incidence by reaching more people at an earlier stage in their disease. In a survey in Bangalore, for example, about 1,000 smear-positive TB patients were asked how many doctors they had visited before being diagnosed with and treated for TB in the public sector. The median number given was three, even though these were relatively easy cases to diagnose and treat. Furthermore, each successive doctor added about 2 weeks to the delay in diagnosis and treatment.

The large volume of anti-TB drugs being disseminated by the private sector suggests that many people being treated for TB are not being notified by the national program. The exact number of patients remains highly uncertain because of a lack of both diagnostic confirmation and standardization in treatment regimens in the private sector. Despite this uncertainty, the public sector lacks a system to track notifications of patients diagnosed and treated in the private sector.

Public-private mix (PPM) initiatives in India and subsequent surveillance have shown that it is possible to reach patients through medical colleges and large NGOs. But these efforts have had less success at reaching private providers. In India, efforts have focused on promoting referrals from the private sector for subsidized diagnosis and treatment. According to surveys, however, relatively few people being treated in public-sector facilities were referred from the private sector. Among the private providers involved with the national DOTS program, most simply provide patients with treatment and adherence information—relatively few diagnose and refer patients meaningfully.

In some countries, private providers are required to notify public agencies about TB cases, with penalties for failure to comply. This is not the case in India, and according to Dewan, even if such laws existed, the country currently lacks enforcement capacity. Beyond the current strategy of exhorting private providers to refer patients to the public sector, two basic approaches have been used to engage and accommodate the private sector in ways that acknowledge and deal with the reality of market forces. First, many countries have tried a collaborative model in which the public sector subsidizes treatments that are then provided by the private sector. In this way, the public sector can ensure that the quality of treatment meets minimum standards. In the second approach, the public sector contracts with private entities to identify and treat TB. Some countries seek to regulate private-sector treatment, require certification or accreditation of private-sector providers, or restrict access to quality anti-TB drugs in ways designed to shape private-sector access. Engaging with the private sector creates a channel for reaching and notifying patients. Furthermore, notification can occur earlier than if a patient comes to the public sector only after visiting one or more private providers.

Dewan suggested that one of the most important effects of successful engagement of India's private sector would be to reduce the inadvertent development of MDR TB driven by nonadherence to international standards of TB care. Beyond MDR prevention, there are many opportunities for engaging the private sector in the direct response to MDR TB, especially with respect to providers who may likely see more drug-resistant TB, such as referral centers and chest physicians. In India, the availability and use of unaccredited DST and second-line anti-TB drugs are widespread. The provision of subsidized treatment for MDR TB is a powerful incentive, but it is not enough for the RNTCP simply to treat MDR TB. The disease must be detected and treated early to reduce transmission. Dewan suggested that the RNTCP consider the possibility of subsidizing private laboratories for early detection of patients seen by private providers for drug-susceptible and drug-resistant TB alike. Strengthening the quality of case management among private providers, including hospitals and medical colleges, also is critical. The cost difference between first-line (lower-cost) and second-line (higher-cost) anti-TB regimens may be a benefit in that patient demand for treatment of MDR TB with fully subsidized, quality-assured second-line drugs could help make inroads into improving private-sector case management for MDR TB.

TECHNOLOGICAL INNOVATIONS IN TB CONTROL³

Using Technology to Involve the Private Sector in Surveillance

Karachi, Pakistan, is a city of 18–20 million people comprising 18 administrative towns. The city had 63 TB diagnostic and treatment centers reporting to the National TB Program in 2010, 33 of which were operated by the government and 30 by private-sector partners. Among the many other health care providers in the city are more than 3,500 private general practitioner (GP) clinics and almost 400 hospitals where patients can be admitted overnight.

These providers can be plotted on a map along with the TB patients being seen by the Indus Hospital TB Program (Figure 7-2), the latter being determined by a GPS coordinate for each patient registered at the hospital. This map illustrates that it is often much easier for a patient to walk to a nearby private clinic than to a TB center, which emphasizes the critical need to involve the private sector in TB case detection and management.

³ This section is based on the presentations of Shelly Batra, President and Cofounder, Operation ASHA, and Aamir Khan, Founder and Executive Director of Interactive Research and Development (IRD) and Director, Indus Hospital Research Center (by teleconference).

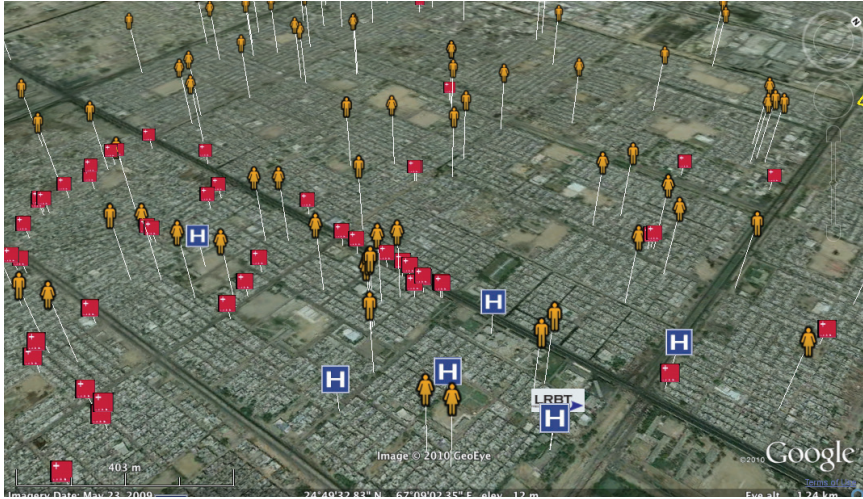


FIGURE 7-2 A map of part of Karachi pinpoints TB patients (small figures), private health care providers (small red squares), and hospitals (boxes containing a capital H).

SOURCE: Khan, 2011.

The map also highlights the benefits of using mobile technologies to capture data efficiently from both the public and the private sectors.

Aamir Khan, Founder and Executive Director of Interactive Research and Development (IRD) and Director, Indus Hospital Research Center, described two open-source software systems being used and further developed by IRD to gather data on the use of public and private providers in Karachi. The first, OpenXdata, uses cell phones to access information from a server while a health worker is visiting a patient's home. A field worker or treatment provider can download data from the server and upload new data on the patient, including basic demographics, laboratory specimens collected, results, whether the patient has MDR TB, and whether the patient is describing any adverse events. This system is an effective and inexpensive tool for health care providers to use when seeing patients in their homes, said Khan.

The second system, OpenMRS, is a medical records system for use on a desktop or laptop computer to access data on a patient from either inside or outside a clinic. Accessible data include bacteriology results, the patient's treatment regimen, the patient's adherence to the regimen, and when the patient was first registered. OpenMRS also provides alerts to support treat-

ment. If a patient with MDR TB was resistant to isoniazid, for example, the system would warn the provider if isoniazid was prescribed.

IRD informatics developers then combined these two systems with a Google Earth interface to visualize what it calls the “TB horizon” in the community. Clicking on any patient using a graphical interface extracts data in real time from the patient’s medical records. The data are summarized for treatment managers to help ensure that patients are receiving DOTS, that they are on the right regimen, and that they come in for their regular smear and culture tests.

IRD received a TB REACH grant in 2010 for the use of mobile phones to provide conditional cash transfers to CHWs and GPs who identify suspected cases of TB, refer them for testing, and ensure that they receive treatment until cure or completion of the regimen is achieved. CHWs and GPs can earn up to 1,000 Pakistan rupees (PKR) for identifying a smear-positive TB case, with the amount of the incentive increasing for successful treatment. Monies are received via the recipients’ mobile devices through existing mobile phone banking systems. Other CHWs perform contact tracing in households of known TB cases and receive similar financial incentives.

The provision of conditional cash transfers via mobile phone resulted in a 100 percent increase in reporting of suspected TB cases to the Indus Hospital TB Program from the first quarter of 2010 to the first quarter of 2011. In addition, support from the Global Fund provides MDR TB patients with monthly food baskets, routine counseling, and other social supports, which serves as an incentive for these patients to complete their treatment. Future plans for the program call for cash transfers to patients based on their record of compliance with treatment.

This program provides a valuable model for engaging the private sector in the treatment of drug-susceptible TB and MDR TB, not just within Pakistan but globally, said Khan.

Using Technological Innovations to Track Patients

Batra described an intriguing, promising effort to use biometric devices for automated compliance tracking. Operation ASHA has deployed the devices at 17 South Delhi centers covering 940 patients and 35,000 transactions. Fingerprints are sent through cell phones to an online repository, whether at a center or a patient’s home. This system has resulted in a default rate of less than 0.5 percent and costs only \$3 per patient. Batra explained that the cost is offset by the time a manager would otherwise have spent developing reports for the government and donors, which are now automated through the tracking system.

POTENTIAL INNOVATIONS AND ACTION ITEMS

Through the presentations provided in this session and the subsequent discussions, individual workshop speakers and participants noted key innovations and action items. They include the following:

- Operation ASHA has created a dense network of treatment centers for MDR TB, conveniently located in community centers that are open for extended hours and protect a patient's privacy.
- Community leaders are involved through the Operation ASHA network to increase active case finding and to maintain parallel records with those of the government. They are offered incentives for case detection and for keeping patients on treatment.
- Cell phones and fingerprint technology are used in the Operation ASHA program in India and in the Indus Hospital TB Program in Karachi, Pakistan. This increases the efficiency of treatment tracking and offers opportunities for improved results.
- In these innovative programs, the community is utilized, and a division of labor and costs among NGOs, families, foundations, and public and private health care providers is devised to reach more patients and improve treatment.

8

Confronting Challenges to the Supply Chain for Second-Line Drugs

Key Messages

- The global marketplace for second-line drugs to treat drug-resistant TB is not operating efficiently or effectively.
- The cost of stockpiling or failing to use second-line drugs demands careful attention because it creates issues with the supply chain.
- Harmonizing quality standards and treatment regimens could attract additional suppliers of second-line drugs, create competition, and reduce prices.
- It could be beneficial to quantify the risks associated with supplying second-line drugs through more effective forecasting, aggregated to reduce country-by-country exposure of suppliers to risk and shared among countries to create a transnational market for these drugs.

MDR TB cannot be controlled without an adequate, uninterrupted supply of second-line drugs. But these drugs are expensive, which means they must be used effectively. Moreover, the markets for these drugs are relatively small and uncertain, making suppliers reluctant to commit resources to their manufacture. The resulting high prices exacerbate shortages and strain national TB programs.

One session at the workshop focused specifically on challenges to delivering quality-assured second-line drugs to patients. Presenters delineated the specific challenges at each step in the supply chain; considered

current methods of drug procurement in India and the implementation of the country's national MDR TB program; described lessons learned from experience with HIV/AIDS initiatives with respect to increasing the number of suppliers and reducing the prices of second-line anti-TB drugs; and explained the need to quantify, aggregate, and share risks to improve the marketplace for second-line drugs.

CHALLENGES IN DRUG SUPPLY CHAIN LOGISTICS¹

DOTS programs have been focused on reducing stockouts, in which drugs become unavailable. Less risk is associated with overstocking first-line than second-line drugs because the former are relatively inexpensive, noted Prashant Yadav, Senior Research Fellow, and Director of Healthcare Research, William Davidson Institute, University of Michigan. For second-line drugs, overstocking can waste scarce financial resources that could otherwise be used for expanding MDR TB programs. At the same time, an uninterrupted supply of second-line drugs is imperative if an MDR TB program is to be successful. MDR TB programs therefore must maintain a fine balance between effectiveness and efficiency.

Yadav highlighted six challenges that arise in the supply chain for second-line drugs, from grant disbursement to distribution. The descriptions below correspond to the challenges numbered 1 through 6 in Figure 8-1.

Uncertainties in the Timing of Grant Disbursement

The flow of funds, whether from a ministry or a Global Fund grant, is often uncertain. When financing is uncertain, procurement planning is difficult. For example, stringent procedures must be followed before Global Fund grants can be disbursed, which often leads to delays in disbursement, said Yadav. Similarly, Ministry of Health budgets often are subject to delays in the release of funds.

Unpublished data show that among the categories of drugs purchased using Global Fund grants, the time gap between planning a purchase and receiving a shipment is greatest for TB drugs. According to Yadav, this gap also is higher in India than in the surrounding region and compared with the global average.

If it is difficult to predict when funds will become available, procure-

¹ This section is based on the presentation of Prashant Yadav, Senior Research Fellow, and Director of Healthcare Research, William Davidson Institute, University of Michigan. (At the time of the workshop, Dr. Yadav was Professor of Supply Chain Management, MIT-Zaragoza International Logistics Program.)

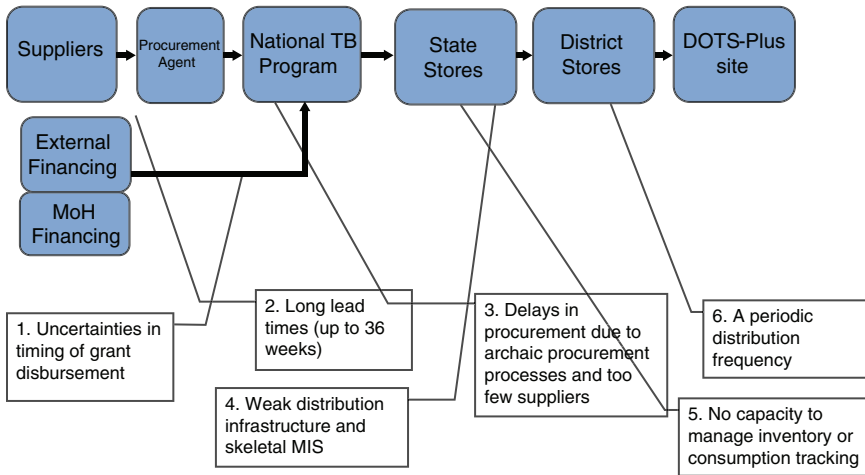


FIGURE 8-1 A schematic of the typical drug supply chain structure, which may not hold for all countries. Challenges in the supply chain for MDR TB drugs extend from grant disbursement to distribution.

NOTE: DOTS = Directly Observed Treatment-Short course; MIS = management information systems; MoH = Ministry of Health.

SOURCE: Yadav, 2011.

ment planning is problematic because the funds must be available before the first steps in the procurement process can occur. This uncertainty is one of the leading causes of national-level stockouts.

Innovative bridge financing arrangements can help alleviate this problem. With such financing, procurement and planning processes need not change because of financial uncertainty. For example, the United Nations Foundation recently initiated a program called the Pledge Guarantee for Health. If a country anticipates a short-term gap in financing that will lead to a stockout in the national program, it can secure bridge financing until the funds become available.

Long Lead Times and Delays in Procurement

Most second-line drug manufacturers employ make-to-order production—they do not start production until final purchase orders are received. Further, some manufacturers procure the active pharmaceutical ingredient (API) for a drug only after receiving a purchase order, and there are very few sources of these ingredients for many second-line drugs. As a result of

these and other factors, the procurement of second-line drugs can take up to 36 weeks after an order has been placed.

Manufacturers cite poor forecasts and small markets as reasons for requiring long lead times and employing make-to-order production. In a market that is uncertain and small—as is the case for many second-line drugs—the manufacturer is unlikely to keep stock on hand.

If national TB programs could provide advance information about their needs to global agencies, lead times would be reduced not just for those programs but for all programs. In this way, sharing advance order information would create a global public good, said Yadav. Countries or international organizations should not be in the business of holding inventory on behalf of manufacturers. The manufacturer could hold a larger inventory of finished product, and short-term imbalances in supply and demand could stabilize. Manufacturers could draw on stockpiles to meet the needs of country programs that were close to stockouts. Inventories should be held strategically to rectify short-term imbalances in high-risk areas.

In addition, delays in procurement can arise from archaic procurement processes and the lack of an adequate number of suppliers. For example, tender regulations often require purchasers to provide additional justification if a fully competitive market does not exist. In this case, having few suppliers not only increases prices but also makes the procurement process more challenging.

Weak Distribution Infrastructure

The distribution infrastructure for second-line drugs often is skeletal, and logistics management information systems (LMIS) beyond the district or state level often are weak. Yadav suggested that programs must learn to distinguish between forecasts and targets. Forecasts frequently are made by specifying coverage targets and then forecasting what quantity of drugs is needed. But going from a target to a forecast also requires considering such factors as consumption data and progress toward achieving a target. Forecasts typically are poor unless they are supplemented by field consumption data. Collecting these data requires synchronizing LMIS and surveillance data, which are generally separate. Especially for MDR TB, these data gathering mechanisms must be carefully coordinated, said Yadav.

Lack of Capacity for Inventory Management or Consumption Tracking

Yadav observed that it is unnecessary for the structure of the second-line drug supply chain to mimic the government's administrative structure. Just because both a state and a district exist does not require that both the state and the district hold stock. Stockholding could be only at the national

level, with no state stores, or it could be at the state level, with no district stores. The key point for consideration is determination of the optimal stocking pattern.

Yadav cited two examples from the retail industry that could hold potential for improving the efficiency and effectiveness of the second-line drug supply chain. First, consumption data from the point of sale are embedded into the planning process at every level of the retail supply chain. This synchronization of data ensures that stock availability remains high. With MDR TB, the equivalent challenge is to collect consumption data at the facility level, preferably through use of user-friendly computerized systems. One system, for example, uses pictures of stock control cards at a facility to compile data, which allows for planning at each stage of the supply system and for high service levels. Second, the retail industry has a high frequency of deliveries. The counterpart for MDR TB would be more frequent deliveries than in the past, which also would counter some of the uncertainties of the market.

INDIA'S SECOND-LINE DRUG SUPPLY CHAIN²

Since the DOTS-Plus program began in India in 2007, guidelines for the diagnosis and treatment of MDR TB and for drug logistics have been established, noted Pradeep Saxena, Director, Central Bureau of Health Intelligence, Directorate General of Health Services, Government of India, and Head, WHO Collaborating Center for the Family of International Classifications, India. The program in India has, however, faced many challenges in providing patients with second-line drugs. Fewer patients than expected have been initiated on MDR TB treatment during the early phase of the program, which has posed the risk of having an excess of second-line drugs. Accurate forecasting of the need for drugs has been difficult, and delays in the provision of drugs have occurred. Ensuring the quality of drugs has been difficult as well, as has been preventing stockouts. Also, second-line drugs have a shorter shelf life than first-line drugs—just 2–3 years as opposed to 5 years.

The RNTCP has responded to these challenges in several ways. It has streamlined identification and referral of suspected cases of MDR TB and introduced rapid diagnostic methods, such as the LPA, which reduce delays in diagnosis and patient attrition. The program also has improved planning

² This section is based on the presentation of Pradeep Saxena, Director, Central Bureau of Health Intelligence, Directorate General of Health Services, Government of India, and Head, WHO Collaborating Center for the Family of International Classifications, India. (At the time of the workshop, Dr. Saxena was Chief Medical Officer, Central TB Division, Government of India.)

for future treatment through data-driven state-level micro-planning that incorporates all aspects of the DOTS-Plus program, including geographic and time-based expansion of services.

In 2010, the RNTCP planned to detect 8,000 MDR TB cases, and drugs for 8,000 patients were procured (Figure 8-2). For 2011, the plan called for detecting 15,000 cases, with a steady increase in future years. The need for second-line drugs can be expected to increase accordingly. Funding for second-line drugs in India has come from the Global Fund Rolling Continuation Channel (RCC) and Round 9, UNITAID, and the World Bank, with the World Bank providing credit for the purchase of drugs.

The Central TB Division is forecasting the need for second-line drugs with technical assistance from partners of the RNTCP, including WHO and the Clinton Foundation. Requirements are being developed for all three weight bands based on past experience, assumptions of weight gain, and an expected prolongation of the intensive phase in many patients. Regular validation of the data is performed, and available stock balances are taken into account in the forecasting. With these techniques, forecasting for future drug requirements has become much more accurate.

To ensure patients' adherence to 2 years of treatment, a large number of community DOTS providers have been trained. Detailed guidelines for the logistics management of second-line anti-TB drugs have been established.

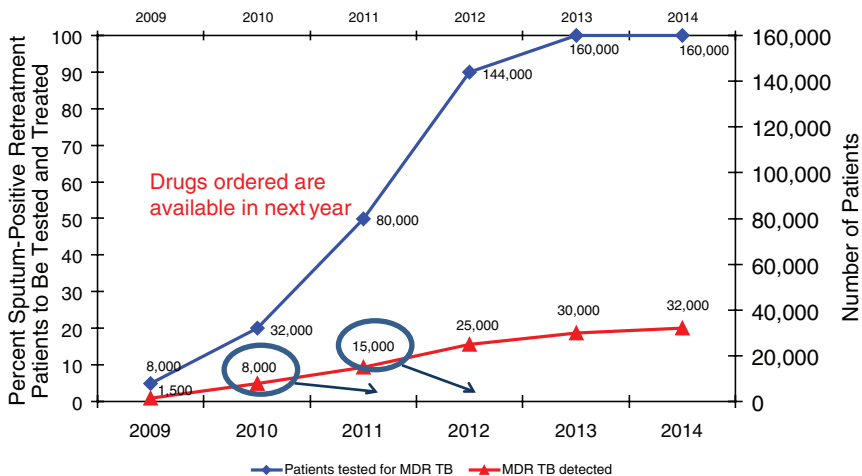


FIGURE 8-2 The Revised National TB Control Program (RNTCP) goals for MDR TB diagnosis call for increasing the number of sputum-positive retreatment patients to be tested and treated in future years.

SOURCE: Saxena, 2011.

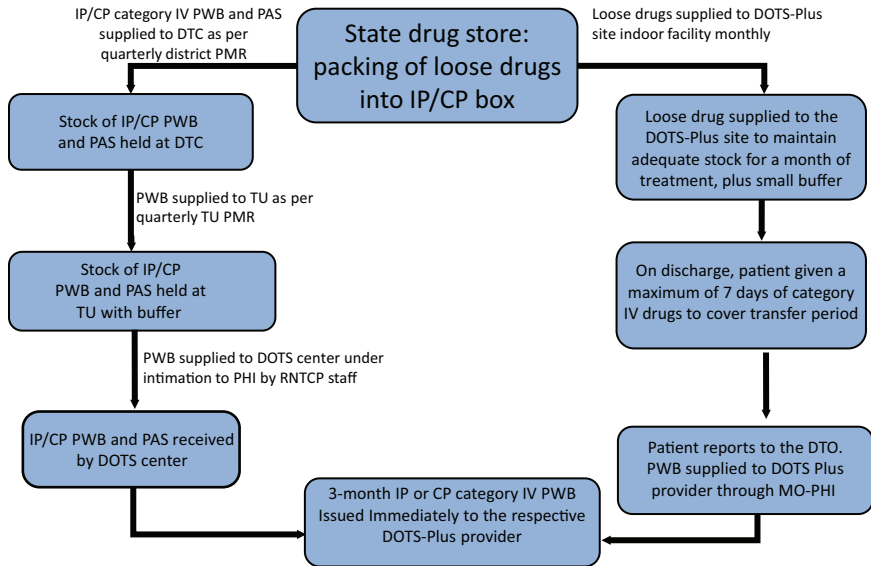


FIGURE 8-3 Second-line drugs move from state drug stores to DOTS-Plus providers through a series of steps.

NOTE: CP = continuation phase; DOTS = Directly Observed Treatment-Short course; DTC = District TB Center; DTO = District TB Officer; IP = intensive phase; MO-PHI = Medical Officer-Peripheral Health Institute; PAS = P-aminosalicylic acid; PMR = Program Management Report; PWB = Patient-Wise Box; RNTCP = Revised National TB Control Program; TU = TB unit.

SOURCE: Saxena, 2011.

And treatment adherence plans have been implemented for NGOs and private practitioners.

Loose drugs are now packed at the state warehouse into 3-month boxes for both the intensive and continuation phases under the guidance of medical officers. Each box is divided into three 1-month segments. A label on the box gives the itemized names of the drugs, the quantities in the box, the batch numbers of the drugs, the expiration dates of the drugs, and an identification number to help track every box. Drugs are then supplied to the DOTS-Plus site and to patients. Figure 8-3 depicts the movement of second-line drugs from the state drug store to patients.

To counter delays in the provision of second-line drugs, the RNTCP procures drugs through two independent sources. For states funded by the Global Fund, the drugs are procured through the GDF by the IDA Foundation after approval from the GLC. For World Bank-funded states, drugs are procured by the procurement agency of the Ministry of Health. Interstate

transfer of drugs also takes place to ensure optimum stock levels in all implementing states at any given time.

Steps are taken to ensure the quality of drugs both at the time of and after procurement. For states funded by the Global Fund, drugs are procured only from suppliers prequalified by WHO, so that high quality standards are maintained. For states funded by the World Bank, drugs are procured through international competitive bidding, with procurement restricted to suppliers compliant with WHO-Good Manufacturing Practice (GMP) guidelines. A joint inspection team under the Drug Controller General of India verifies the WHO-GMP certificates and performs predispatch inspection of all batches. After procurement, an independent International Organisation for Standardization (ISO) 17025-certified laboratory conducts quality testing of drugs. In addition, storage guidelines ensure maintenance of proper temperature and humidity.

To prevent stockouts, monthly reports from implementing states and quarterly reports from states and districts allow for regular monitoring of drug stocks. An information system for second-line drugs also is in place, with reports moving from the subdistrict to the district to the state level and on to the Central Division.

Finally, to address the shorter shelf life of second-line drugs, drugs come in three tranches instead of the usual two to ensure their full use. The Central Division also regularly monitors second-line drug stocks in state drug stores.

Taken together, these steps have had many positive benefits, said Saxena. They have improved planning for the future numbers of MDR TB patients to be diagnosed and placed on treatment. Having more than one source of second-line drugs ensures uninterrupted supplies. Drug logistics guidelines are dynamic and are revised according to new experiences from the field. Stock status is reported regularly to higher levels by subdistrict, district, and state drug stores. As a result of these steps, the RNTCP has been able to prevent stockouts in the concerned states.

Taking the steps described above has provided valuable lessons for program managers and others, said Saxena. The lessons learned from India's experience in responding to the challenges of supplying second-line drugs include the following:

- Plan for the number of MDR TB patients to be diagnosed and treated in the future.
- Have more than one source of second-line drug supplies if possible.
- Implement drug logistics guidelines.
- Monitor drug stocks regularly.
- Provide training for field staff.
- Conduct supervisory visits and frequent consultations with state and district officials.

IMPROVING THE AVAILABILITY AND REDUCING THE COST OF MDR TB DRUGS³

The availability of second-line drugs in India is problematic, said Inder Singh, Executive Vice President of Access Programs, Clinton Health Access Initiative. Five of nine second-line drugs could not be awarded in India's 2009-2010 World Bank tender. The fact that only about 3,600 of 5,400 diagnosed MDR TB patients actually started treatment was due partly to the lack of second-line drugs. And the drugs are expensive, costing \$4,400 or more per patient as compared with \$19 for first-line drugs.

Coordinated actions can improve the availability and dramatically reduce the price of WHO-prequalified drugs for MDR TB in the near to mid-term, according to I. Singh. Today, the demand for certain drugs is below a key threshold, leading to a natural monopoly, he said. Exceeding this threshold would enable the sustainable entry of additional suppliers and the application of market dynamics.

To improve availability and reduce prices, demand must grow, said I. Singh. One way to create new demand is to invest in case finding for MDR TB, and considerable work is being done in this area. A second way to increase demand is to harmonize quality standards across key buyers. I. Singh noted that virtually no work is being done in this second area.

I. Singh described several case studies drawn from HIV/AIDS initiatives that could be applied to MDR TB. Price remains a barrier to access to antiretroviral therapy for HIV/AIDS. Yet, the price of one important drug for HIV/AIDS, tenofovir, dropped by more than 58 percent between 2006 and 2010. The price reduction was achieved through a variety of strategies, including finding new suppliers, using less expensive inputs, and developing new processes.

In a second case study, advanced procurement practices expanded the supply base and reduced supply risks, thereby reducing prices. An important HIV/AIDS drug had been selling at \$500 for 10 years, and the developer of that drug had said no other company in the world could produce it according to quality standards. After 30–50 percent of the global volume of demand for this drug was allocated to any second supplier that could meet quality standards, regardless of price, a generic supplier entered at a price higher than that of the developer. Over the course of several years, however, the second supplier reduced the price of the drug dramatically, and the developer has now, in turn, reduced the price to be competitive. As a result of this approach, three generic manufacturers now meet WHO prequalification standards for the drug.

Finally, I. Singh cited a case in which the Clinton Health Access Initia-

³ This section is based on the presentation of Inder Singh, Executive Vice President of Access Programs, Clinton Health Access Initiative.

tive worked with suppliers to avoid supply disruptions. In the first half of 2010, an impending global supply shortage of tenofovir loomed. By providing suppliers with data on the impending shortage and emphasizing both the business and the humanitarian opportunities, the foundation persuaded three suppliers to expand their production capacity significantly.

In the area of MDR TB, growth in demand is essential before these approaches can be applied to bring new suppliers into the marketplace. Demand must grow by factors of 2 to 10 for several second-line drugs to support the entry of additional suppliers, create competition, and reduce prices, said I. Singh. Today, different quality standards effectively create distinct markets for the same drug. Similarly, different treatment regimens fragment the market. Harmonizing both quality standards and treatment regimens could boost demand, said I. Singh, creating opportunities for dramatic price reductions for two or even three of the second-line drugs.

MOVING TOWARD A FUNCTIONAL MARKET FOR SECOND-LINE TB DRUGS⁴

Owen Robinson, Partnerships Manager, Mirebalais National Teaching Hospital, Partners In Health, discussed the relationship between management of MDR TB drugs and a strong, quality-assured drug marketplace. A strong drug management strategy can manage risk, lower price, and increase availability, but such a strategy must be global in scope, he said.

A healthy marketplace for MDR TB drugs has several cycles. As case finding takes place more quickly, patients are enrolled more quickly, and drug orders increase. Also, as higher volumes of drugs are needed, iterative negotiations can lower prices. These two processes can reinforce each other, with a larger market potential resulting from higher enrollment and higher enrollment capacity resulting from price reductions.

However, the marketplace for second-line TB drugs is largely stalled at present. Case finding is limited by low drug stocks, and drug orders are limited by low case finding. Suppliers opt not to scale up because of historically low order volumes, and orders remain low because of high prices. The supply side is averse to the risk of making drugs that will not be purchased, while the demand side is averse to the risk of purchasing drugs that will not be used.

The application of three principles can help manage risk in the MDR TB drug marketplace, said Robinson. First, risks need to be quantified, which allows everyone to understand what the risks are. Second, risks

⁴ This section is based on the presentation of Owen Robinson, Partnerships Manager, Mirebalais National Teaching Hospital, Partners In Health.

need to be aggregated, at the global level if possible. Third, risks need to be shared among the different entities involved in the transaction.

In the past, risk has been quantified by summing target-based forecasts, such as Global Fund targets for quality-assured procurement. However, these forecasts often fail to materialize because of barriers within countries and at the global level. As a result, suppliers become unwilling to risk their money on the basis of these forecasts. To change this dynamic, countries must consider such risk factors as funding availability, case finding rates, drug sensitivity trends, and programmatic hurdles to arrive at risk-adjusted analyses. Internally, these analyses can allow for optimal ordering processes. Externally, they enable market transparency by supplying providers with information about likely demand.

Once risk has been quantified and placed in the context of risk factors, it must be aggregated internationally, not just country by country. This aggregation can smooth out fluctuations in overall demand, much as investing in mutual funds can smooth out returns by masking the ups and downs of individual stocks. Key requirements for aggregating risk include a centralized aggregating entity; a credible global forecasting mechanism marked by two-way information flows; and a virtual rotating stockpile, in which one country can shift its supplies to another if it does not meet its projections for drug consumption. This approach relies on coordination among countries rather than centralized control of drug procurement. It is complementary to the market leverage associated with aggregating orders across countries and provides greater ability to negotiate lower prices.

Finally, when risk has been quantified through more effective forecasting and aggregated to reduce country-by-country exposure to risk for suppliers, it must be shared between buyer and seller. One way to accomplish this is through payment structures that use such mechanisms as initial upfront deposits, regardless of whether orders materialize; sales guarantees; or the option to purchase later at a certain price. Another approach is to negotiate around lead times using such levers as predictable cyclical orders instead of piecemeal ordering and capacity reservation. Contract terms can provide incentives for new entrants or rely on specified time horizons. Other incentives include reducing barriers to entry and helping with registration issues in different countries.

Robinson posed several important questions to be considered in efforts to improve the second-line drug supply chain:

- Who is involved in these processes, both within each country and globally?
- What is the right role for procurement mechanisms within individual countries?

- What is the right role for the procurement agencies that are involved today?
- What is the right balance between allowing countries to place their own orders and being coordinated enough to mitigate risk factors?
- What informational, human, and organizational resources are required?

DISCUSSION

During the discussion period, Salmaan Keshavjee, Harvard Medical School, talked about the factors that lead to incorrect forecasts of demand. The estimate of 440,000 people with MDR TB is one factor. Countries know they have large numbers of MDR TB patients but are unable to implement programs to reach them. Some people have seen the GLC as a bottleneck. As of the end of 2009, however, the GLC had approved treatment for 80,000 patients, yet countries had implemented only 22,000 treatments. The capacity of countries to implement MDR TB scale-up, a complex health intervention, has been lacking, said Keshavjee.

Part of the solution is to help create demand, Keshavjee continued. Countries with weak health systems need assistance in implementing programs to treat patients. In the past, a lack of rapid and inexpensive diagnostics made it difficult to increase demand, but successful efforts to build laboratory capacity have helped alleviate this problem. Now better systems are needed to procure drugs for and treat diagnosed patients.

Robinson noted that in some countries, the necessary level of transparency has been difficult to achieve for cultural reasons. These countries may have had difficulty with inviting international partners to work in the country, or they may have been reluctant to change past practices. Robinson suggested that there is now an increasing sense of transparency around the issues, as well as greater willingness to work with partners to strengthen forecasting and think strategically.

Puneet Dewan, WHO, remarked that five countries—Brazil, China, India, Russia, and South Africa—account for a large percentage of the world's MDR TB patients. Yet several of these countries operate at least partially outside the system for procuring Global Fund-supported prequalified products. Thus these countries' demand is fragmented into separate procurement mechanisms driven by in-country sources. Unless these countries consolidate their demand, volumes will remain so low that the ultimate goals of stable supply, stable manufacturers, and price reductions are unlikely to be achieved.

Robinson pointed to an analysis of first-line drugs conducted by the Clinton Health Access Initiative that found that countries procured prequalified drugs only when they were forced to work through the GDF mecha-

nism as a condition of the funding they were receiving. When they were using their own funding or were large enough to make their own demands, they opted for alternative ways of procuring first-line drugs. The result was what Robinson characterized as a missed opportunity for both quality control and aggregation of demand. The situation is similar for second-line drugs, he said. If countries are forced to channel their orders through a centralized mechanism as a condition of funding, they will do so; otherwise, they will do what is most convenient for them. Robinson suggested that the latter countries must have incentives for aggregation of demand. To that end, it is important to meet their needs in a way they find acceptable, as well as to explain the benefits of aggregation.

Saxena noted that national governments need to consider not only the quality and pricing of drugs but also availability and delays. A 4-month delay in accurate diagnosis can result in the loss of 40 percent of identified patients, which contributed to India's being able to initiate only 3,600 of 5,400 identified patients on treatment. If drugs are not available for 12 or 24 months after diagnosis, the losses will be even greater. Consolidating demand around a single quality standard would integrate the market, said Saxena, which should improve lead times dramatically.

Nigorsulton Muzafarova, GDF, WHO Regional Office for Southeast Asia, cited the general scarcity of APIs for second-line drugs discussed by Yadav in his presentation—a major issue for producers of second-line drugs. Muzafarova noted that a drug manufacturer's decision to seek WHO prequalification is complicated by underlying concern about the possibility that one of these critical ingredients is lacking.

Yadav noted that the industry relies on heavy investments, and the individual treatment price does not matter as much as aggregated volumes. Manufacturing, from the point of acquiring raw materials to the point of delivery, tends to be complex and to require a long time. Given the risk involved, moreover, few drug manufacturers are willing to initiate the process until they have an order in hand, and they tend to wait until they have an adequate number of orders collected to begin making one batch. Reducing risk and providing manufacturers with accurate forecasts would probably reduce the time to delivery significantly, said Yadav. I. Singh added that manufacturers are more likely to produce drugs when they can do so on a continuous basis, not for a product that is made in one or two batches per year.

POTENTIAL INNOVATIONS AND ACTION ITEMS

Through the presentations provided in this session and the subsequent discussions, individual workshop speakers and participants noted key innovations and action items. They include the following:

- Given delays in payment, the production and shipment of second-line drugs are often delayed. Bridge financing can offer a solution in the short term. Initial up-front deposits, guaranteed order volumes, options pricing, and the ability to purchase later are all innovative ideas for addressing current challenges in supply chain financing.
- Supply chains can be improved by forecasting future utilization through data-driven state-level micro-planning; incorporating DOTS-Plus geographic, time-based expansion of services; and increasing laboratory capacity.
- Maintaining transparency of information and data with suppliers can drive down costs.
- The harmonization of quality standards to create a homogeneous marketplace has the potential to create demand at a sufficient level of quality.
- Aggregating risk by global ordering, rather than country-by-country ordering, would improve the supply chain as part of a global architecture that would innovate drug procurement procedures.
- A virtual rotating stockpile may help prevent stockouts.
- Effective forecasting would help quantify risk.

9

Creating a Blueprint for Action

In the final session of the workshop, moderators and speakers from earlier sessions summarized the major themes that emerged from their sessions and the actions recommended by speakers. This chapter draws on those remarks and on previous chapters in this summary to outline a blueprint for action to guide future decisions, organized by major topics discussed at the workshop. The conclusions and recommendations presented in this chapter were offered by the speakers identified in parentheses in the text and do not represent the consensus of the group or of the conveners of the workshop.

DRUG-RESISTANT TB IN INDIA

India has been conducting an “amazing” expansion of MDR TB treatment with the goal of achieving universal access to treatment, said Salmaan Keshavjee, Harvard Medical School. The country is using primarily an ambulatory model of care delivery with very short hospital stays. Keshavjee emphasized that achieving national goals in India will require strengthening the health care system. Important steps are to build laboratory capacity, recruit and continually train staff, and reorganize the system to deliver care to MDR TB patients.

Initial results from Gujarat discussed at the workshop were “worrisome,” according to Keshavjee. Resistance to the fluoroquinolones was high at 24 percent. High death rates among some patients suggest late case detection, and high default rates suggest problems with the delivery of treatment. On the other hand, Vishwa Mohan Katoch, ICMR, noted that India has in the past had success in tackling major diseases, such as leprosy, despite

its large population and socioeconomic disparities. With regard to leprosy, there was not only success in reducing the numbers of affected people, but also a reduction and near elimination of drug resistance through implementation of a regimented program.

Conclusions and recommendations offered by individual workshop participants regarding drug-resistant TB in India included the following:

- The overall public health care system in India needs to be strengthened to support a strong anti-TB program. (K. Srinath Reddy, Public Health Foundation of India)
- All TB patients should have equitable access to care, and their interests and needs should be protected. (Reddy)
- The basic TB program in India needs to reach out to unnotified and missed cases and to poor and highly vulnerable populations. (Reddy)
- TB medicines should be sold by prescription only and should be prescribed and dispensed by accredited public and private providers. (Reddy)
- A catalog of TB-related activities in India should be undertaken to take stock of the quality and quantity of these activities. Unproductive or ineffective activities should be rejected to make room for innovative new approaches. (Several workshop participants)

PREVENTING TRANSMISSION OF DRUG-RESISTANT TB

As long as people with drug-resistant TB remain untreated or inadequately treated, they have the potential to transmit the disease to others. Infection control in health care facilities and in the community is essential to stop the spread of the epidemic.

Much remains unknown about both the evolution of drug resistance in *M.tb.* and the transmission of drug-resistant strains among individuals. Certain strains of MDR TB predominate in different countries and regions. An interesting question, said Keshavjee, is whether these strains are more or less fit than other strains in these regions.

Conclusions and recommendations offered by individual workshop participants in the area of preventing transmission of drug-resistant TB included the following:

- Infection control and patient management remain inadequate in many countries. (Keshavjee)
- Treatment should start as early as possible to reduce transmission. (Edward Nardell, Harvard Medical School)

- The potential of surgery to reduce the transmission of TB should be explored. (Rohit Sarin, LRS Institute of Tuberculosis and Respiratory Diseases)
- More research is needed on the fitness and potential for transmission of drug-resistant strains of *M.tb.* (Sébastien Gagneux, Swiss Tropical and Public Health Institute and University of Basel)

STRENGTHENING LABORATORY CAPACITY

The ability to combat drug-resistant TB is limited by the lack of reliable, quality-assured laboratory tests capable of detecting drug resistance rapidly to support patient management decisions, said Thomas Shinnick, CDC. As Prakash N. Tandon, INSA, observed, a 100 percent sensitive and specific test for TB in general and MDR TB in particular still does not exist, and current tests are cumbersome, costly, and difficult to use widely. Some workshop participants also suggested that although the ideal diagnostic test has yet to be developed, more focused and effective efforts should be undertaken to identify MDR TB using current diagnostics.

India is making good progress in improving laboratory capacity by expanding access to quality-assured conventional and molecular testing, and it is taking advantage of new technologies that are being developed, said Shinnick. But much more work needs to be done to expand the ability of patients to access laboratory services. Rapid tests are promising, but are not yet sufficient to address the problem. The time between ordering a test and implementing a patient management decision based on that test must be minimized. To this end, close communication and coordination among clinicians, TB program managers, laboratory managers, and others will be necessary.

Conclusions and recommendations offered by individual workshop participants with regard to strengthening laboratory capacity included the following:

- In resource-limited settings, standardized treatment regimens rather than individualized regimens may be necessary. (Sarin)
- India needs to strengthen its laboratory capacity with a tiered network at the subdistrict, district, regional, and reference laboratory levels. (Camilla Rodrigues, Hinduja Hospital)
- Validation, quality assurance, and quality control all are essential for DST. (Shinnick)
- Supranational reference laboratories must have the resources and expertise to survey drug resistance and conduct external quality testing for drug susceptibility tests. (Nagamiah Selvakumar, National Institute for Research in Tuberculosis)

- DST laboratories in India need to maintain their proficiency despite shortages of second-line drugs. (Neeraj Raizada, FIND)

ADDRESSING TB AND DRUG-RESISTANT TB IN VULNERABLE POPULATIONS

Children, people infected with HIV, and migrant and refugee populations all are especially vulnerable to drug-resistant TB and can contribute to its spread. The incidence of drug-resistant TB in these populations remains unknown, especially among children, and this lack of information obscures the extent of the problem. But contact tracing has revealed large numbers of TB and MDR TB cases arising within and from these populations.

Another important vulnerable population, noted Gary Filerman, Atlas Health Foundation, is the prison population. Although the incarcerated and others in congregate settings were not discussed extensively at the workshop, Filerman and Keshavjee noted that the prison populations in almost every country have higher rates of TB and MDR TB than the general population and deserve special attention.

Conclusions and recommendations offered by individual workshop participants in the area of addressing TB and MDR TB in vulnerable populations included the following:

- The burden of drug-resistant TB in vulnerable populations needs to be documented. (Soumya Swaminathan, National Institute for Research in Tuberculosis)
- Better diagnostics are especially important for pediatric populations. (Swaminathan)
- New technologies that can deliver results of DST rapidly for children and people coinfecting with HIV are a particular need. (Keshavjee)
- Shorter treatment regimens for MDR TB may be possible in children because of their lower bacillary burden, but clinical trials are needed to test this hypothesis. (Swaminathan)
- New drugs being developed for adult TB patients should be studied in children early in the development process so that pediatric populations can have access to these drugs as quickly as possible. (Swaminathan)
- The possibility of using first- and second-line drugs prophylactically to prevent TB infection in children and other vulnerable populations needs to be studied. (Swaminathan)
- Vulnerable populations and their contacts should be eligible for more aggressive testing. (Mercedes Becerra, Harvard Medical School)

- A global project on pediatric MDR TB could produce much more information about a population that also acts as a sentinel population for infection and treatment issues. (Becerra)¹

COMBATING DRUG-RESISTANT TB THROUGH PUBLIC-PRIVATE COLLABORATION AND INNOVATIVE APPROACHES

The majority of people in India access private-sector health care services, which means that engaging private health care providers in the fight against MDR TB is essential. In addition, the volume of anti-TB drugs being disseminated by the private sector suggests that many people being treated for TB are not being recorded by public-sector providers. Some second-line drugs are widely available outside the public-sector program. Conclusions and recommendations offered by individual workshop participants on this subject included the following:

- Private-sector laboratories need to be incorporated into the public health laboratory network so they will become an integral part of the national TB control program. (Puneet Dewan, WHO)
- Opportunities to subsidize private laboratories for the early detection of drug-resistant TB should be explored. (Dewan)
- The quality of the case management performed by private providers needs to be improved. (Dewan)
- Private laboratories should be reimbursed, at cost, for drug-susceptibility testing so that these savings can be passed on to patients. (Rodrigues)

Strengthening the Workforce

Human resources to carry out drug-susceptibility testing, MDR TB treatment, and other activities associated with drug-resistant TB are severely limited in India. Coordination of training between the public and private sectors could ease shortages and improve skills. Speakers offered the following conclusions and recommendations on strengthening the workforce:

¹ Since the workshop, Mercedes Becerra, Assistant Professor, Department of Global Health and Social Medicine, Harvard Medical School, and Soumya Swaminathan, Head, Division of Clinical Research, National Institute for Research in Tuberculosis, collaborated to launch a research network on pediatric drug-resistant TB. As of April 2012, more than 140 individuals from more than 30 countries had come together to collaborate on joint projects through the network, titled The Sentinel Project on Pediatric Drug-Resistant Tuberculosis. More information is available at <http://sentinel-project.org/> (accessed April 30, 2012).

- Health workers at all levels need training, retraining, on-the-job training, continuing education, and advanced management training. (Aleyamma Thomas, National Institute for Research in Tuberculosis)
- Training should be followed by in-service monitoring and supervision to detect performance deficiencies, identify new staff in need of training, and identify additional staff needed for current and new interventions. (Thomas)

Using Innovative Technologies

Technology—whether cell phones, electronic medical records, laptops, or biometric identification systems—can facilitate better MDR TB treatment, said Janet Tobias, President, Sierra/Tango Productions, Ikana Media. These technologies can connect health care providers, laboratories, and patients so that treatment can start earlier and be more effective. These technologies also make it possible to offer incentives to private providers and CHWs for identifying MDR TB patients and ensuring that they receive treatment. In addition, technologies make it possible to collect and analyze data that can shape policy decisions and improve patient outcomes. Conclusions and recommendations offered by individual workshop participants regarding the use of technology included the following:

- Pilot programs involving technology should be carried out with health care providers and TB patients to explore ways of expanding treatment. (Tobias)
- Technological interventions in TB care are needed and can go beyond data collection to increase the number of patients identified and improve patient outcomes. (Several workshop participants)
- Economic analyses of the costs of MDR TB and the value of treatment could help make the case to governments for the need to invest in efforts to combat drug-resistant TB. (Tobias)
- Patients should be full partners in drug-resistant TB programs. (Tobias)
- Low-cost, high-impact community-driven models are needed to deliver testing and treatment in difficult-to-reach areas. (Shelly Batra, Operation ASHA)

Creating Partnerships

A recurring sentiment expressed at the workshop was that, given the incidence of MDR TB in India and elsewhere, partnerships are essential to bring the combined resources of multiple organizations to bear on the

problem. Partnerships are needed among various government levels within India, between the public and private sectors, and among international organizations. Finally, patients must become partners with health care providers and governments to win the battle against MDR TB. Conclusions and recommendations offered by individual workshop participants with respect to creating partnerships to combat MDR TB included the following:

- International partnerships and assistance are essential to address MDR TB in resource-limited settings. (Keshavjee)
- INSA should continue to collaborate with other national science academies, including the IOM and National Academy of Sciences, to reduce the threat of drug-resistant TB. (Krishan Lal, INSA)
- Science academies from around the world should convene to develop consensus around actions needed to combat drug-resistant TB. (Tandon)

STRENGTHENING THE SECOND-LINE DRUG SUPPLY CHAIN

Demand for second-line drugs remains too low to sustain multiple suppliers, observed Owen Robinson, Partners In Health. As a result, the prices for these drugs are too high, which is an obstacle to treatment, as are today's long lead times for the production of drugs. Volume needs to rise to spur competition and lower prices. Financial guarantees or other mechanisms could bring additional suppliers into the market.

Conclusions and recommendations offered by individual workshop participants in the area of strengthening the second-line drug supply chain included the following:

- More manufacturers of quality-assured second-line drugs are needed to lower prices and ensure availability. (Keshavjee)
- Demand for quality second-line drugs needs to be adequately forecast and then aggregated to generate the necessary investments by suppliers. (Robinson)
- Risks need to be aggregated and shared throughout the drug supply chain. (Robinson)
- Prequalification procedures and standards need to be harmonized among countries to reduce barriers to entry into the second-line drug market. (Robinson)
- A working group should be formed to explore challenges to the drug supply chain, ways of overcoming current problems, and possible revolutionary rather than evolutionary changes in the drug supply system. (Robinson)

- Best practices from the retail industry could be adapted to manage the inventory and distribution of second-line drugs. (Prashant Yadav, University of Michigan)
- Drug logistics guidelines are needed for the drug distribution network. (Pradeep Saxena, Government of India)

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Appendix A

Workshop Agenda

FACING THE REALITY OF DRUG-RESISTANT TUBERCULOSIS IN INDIA: CHALLENGES AND POTENTIAL SOLUTIONS

April 18-19, 21, 2011
Indian National Science Academy
New Delhi, India

Background

The increasing burden of drug-resistant tuberculosis (MDR TB/XDR TB) introduces new challenges to traditional TB control and treatment programs and calls upon the global health community to collaborate and share scientific information in new and different ways. This 2-day workshop is sponsored by the Forum on Drug Discovery, Development, and Translation of the U.S. National Academy of Sciences, the Institute of Medicine (IOM), the Indian National Science Academy (INSA), and the Indian Council of Medical Research (ICMR). The workshop is the third in a series of international workshops convened by the U.S. IOM. The objectives of the workshop series are:

- The multi-disciplinary workshops span a wide spectrum of issues pertaining to the science and policy around drug-resistant tuberculosis—from biology, epidemiology, and surveillance; to diagnosis, treatment, and infection control; to issues pertaining to the drug supply chain, laboratory capacity, and needs of vulnerable populations. Each workshop will address some or all of these multiple disciplines and facilitate discussion about a broad “blueprint for action.”
- The workshops are an opportunity to present promising new research and also to identify specific gaps in knowledge calling for more research, funding, and international attention.

- The workshop series is being hosted over a period of several years, which will create a venue and body of knowledge that can explicitly consider and address developments over a period of a few years, thus permitting relatively quick adjustments in knowledge and strategy.
- The workshop series convenes international experts, permitting exchange of information among experts from each of the participating countries and globally.
- Each workshop in the series will result in publication by the U.S. National Academies of a summary document that reports the proceedings from each country-specific workshop.

This workshop in New Delhi will address the current status of drug-resistant tuberculosis in India and across the globe; highlight key challenges to controlling the spread of drug-resistant strains; and discuss innovative strategies to advance and harmonize local and international efforts to prevent and treat drug-resistant TB.

DAY 1

8:30-9:00 a.m. Registration and Tea

Welcomes, Background, and Workshop Objectives

9:00-9:40 a.m. KRISHAN LAL
Indian National Science Academy

GAIL CASSELL, *Forum Co-Chair*
Harvard Medical School
Infectious Disease Research Institute

PRAKASH N. TANDON
Indian National Science Academy

VISHWA MOHAN KATOCH
Indian Council of Medical Research

Keynote Addresses

9:40-10:00 a.m. ASHOK KUMAR
Revised National TB Control Program (RNTCP)
Ministry of Health and Family Welfare

- 10:00-10:20 a.m. K. SRINATH REDDY
Public Health Foundation of India
- 10:20-10:40 a.m. *Setting the Stage: Global Challenges and Potential Solutions*

SALMAAN KESHAVJEE
Harvard Medical School
- 10:40-11:05 a.m. Tea Break

SESSION I: DRUG-RESISTANT TB IN INDIA

Session Objectives:

- Provide an introduction to the global challenge of drug-resistant TB and consequences of inaction.
- Describe the epidemiology of drug-resistant TB in India.
- Describe the drug-resistant TB risk factors and provide in-country perspectives of the issues and current strategies for prevention and control.

Session Chair:

- Salmaan Keshavjee, Harvard Medical School

National Scale-Up of Drug-Resistant TB Diagnosis and Treatment

- 11:05-11:20 a.m. KULDEEP SINGH SACHDEVA
RNTCP
Ministry of Health and Family Welfare

Overview of Drug-Resistant TB in India

- 11:20-11:35 a.m. PROF. S. K. SHARMA
All India Institute of Medical Sciences (AIIMS)

- 11:35-11:50 a.m. *Improving Health System Performance to Address the Challenge of Drug-Resistant TB*

ALEYAMMA THOMAS
Tuberculosis Research Centre, Chennai

11:50a.m.- Lunch
1:15 p.m.

SESSION II: GLOBAL BURDEN OF DRUG-RESISTANT TB

Session Objectives:

- Report on findings from previous IOM workshops in South Africa and Russia.
- Present the latest epidemiological and laboratory data describing the estimated burden of drug-resistant TB worldwide, with a focus on high-burden countries other than India (e.g., South Africa, China, and Russia).
- Highlight differences and different trajectories of the drug-resistant TB epidemic globally.

Session Chair:

- Gail Cassell, Harvard Medical School and Infectious Disease Research Institute

1:15-1:45 p.m. *Overview of Findings from IOM Workshop Series*
China data provided by Mingting Chen, Centers for Disease Control

GAIL CASSELL
Harvard Medical School
Infectious Disease Research Institute

1:45-1:55 p.m. *Overview of Global Drug-Resistant TB Burden*
WHO data provided by Matteo Zignol and presented by:

SALMAAN KESHAVJEE
Harvard Medical School

1:55-2:00 p.m. *Updates from Other Countries*

GAIL CASSELL
Harvard Medical School
Infectious Disease Research Institute

SESSION III: PREVENTING TRANSMISSION OF DRUG-RESISTANT TB

Session Objectives:

- Provide an overview of the molecular evidence for transmission of drug-resistant TB.
- Discuss the background and rationale for India's Revised National TB Control Program methods to prevent transmission of drug-resistant TB and the program's future goals.
- Discuss the genetic evolution of *M.tb.* and current best practices in infection control.

Session Chairs:

- Edward Nardell, Harvard Medical School/Partners In Health
- Ashok Kumar, RNTCP

- 2:00-2:15 p.m. ***Importance of Engaging the Private Sector in MDR TB Prevention and Case-Finding***
- PUNEET DEWAN
WHO
- 2:15-2:30 p.m. ***Drug-Resistant TB Transmission and Reactivation/Reinfection Phenomenon***
- S. SIVA KUMAR
Tuberculosis Research Centre, Chennai
- 2:30-2:45 p.m. ***Indian Program Efforts to Prevent Transmission of Drug-Resistant TB***
- PRAHLAD KUMAR
National Tuberculosis Institute, Bangalore
- 2:45-3:00 p.m. ***Population Ecology and the Genetic Evolution of *M.tb.****
- SÉBASTIEN GAGNEUX
Swiss Tropical and Public Health Institute

3:00-3:15 p.m. ***TB Infection Control Reconsidered: The Impact of Treatment on MDR TB Transmission***

EDWARD NARDELL
Harvard Medical School/Partners In Health

3:15-3:30 p.m. ***Roundtable Discussion***

Open Discussion with Workshop Participants

3:30-3:45 p.m. Tea Break

SESSION IV: RAPID METHODS OF DETECTING DRUG RESISTANCE AND STRENGTHENING OF LABORATORY CAPACITY

Session Objectives:

- Provide an overview of current diagnostic methods and identify gaps/current needs that are not being met with tests in use today.
- Consider the next generation of TB diagnostics (e.g., level of resistance that will be detected, use of a test at the point of patient care, specimen processing).
- Consider the validation of diagnostic tests and other quality assurance measures.

Session Chairs:

- Thomas Shinnick, U.S. Centers for Disease Control and Prevention (CDC)
- Sarman Singh, AIIMS

3:45-4:00 p.m. ***Treatment of Drug-Resistant TB***

ROHIT SARIN
Lala Ram Sarup Institute of Tuberculosis and
Respiratory Diseases

4:00-4:15 p.m. ***Diagnosis of Drug-Resistant TB***

CAMILLA RODRIGUES
Hinduja Hospital and Medical Research Center

4:15-4:40 p.m. *Moving Towards the Next Generation of Diagnostic Tests for Drug-Resistant TB: Quality Assurance Considerations in the Development of New Diagnostics*

THOMAS SHINNICK
Division of Tuberculosis Elimination
U.S. Centers for Disease Control and Prevention
(CDC)

4:40-5:00 p.m. *Supranational Reference Laboratory and Private Laboratories in RNTCP*

NAGAMIAH SELVAKUMAR
Tuberculosis Research Centre, Chennai

5:00-5:15 p.m. *Laboratory Capacity in India for the Diagnosis of Drug-Resistant TB: Update on EXPAND-TB Efforts*

NEERAJ RAIZADA
Foundation for Innovative New Diagnostics (FIND)

5:15-5:45 p.m. *Roundtable Discussion*

Open Discussion with Workshop Participants

DAY 2

SESSION V: REACHING VULNERABLE POPULATIONS AFFECTED BY DRUG-RESISTANT TB

Session Objectives:

- Discuss ways to address priorities of reaching and treating drug-resistant TB patients in the large Indian population.
- Present data on the burden of drug-resistant TB and treatment methods in vulnerable populations such as children, migrants, refugees, and HIV-infected populations.

Session Chairs:

- Mercedes Becerra, Harvard Medical School
- Soumya Swaminathan, WHO¹

9:00-9:15 a.m. ***Addressing Drug-Resistant TB in Pediatric Populations***

SOUMYA SWAMINATHAN
WHO

9:15-9:30 a.m. ***Burden of Pediatric Tuberculosis in Households of Patients with MDR TB***

MERCEDES BECERRA
Harvard Medical School

9:30-10:00 a.m. ***Drug Resistance in India's HIV-Infected Population***

DIGAMBAR BEHERA
Lala Ram Sarup Institute of Tuberculosis and
Respiratory Diseases

Drug-Resistant TB in Migrant and Refugee Populations

KUNCHOK DORJEE
Tibetan TB Control Programme, Department of
Health, Tibetan Government in Exile

10:00-10:30 a.m. ***Roundtable Discussion***

Facilitator: Anne Goldfeld, Global Health
Committee/Cambodian Health Committee, Harvard
Medical School

10:30-11:00 a.m. Tea Break

¹ At the time of the workshop, Soumya Swaminathan was Coordinator for Neglected Priorities Research with the WHO's Special Programme for Research and Training in Tropical Diseases. Since the workshop, Swaminathan has rejoined the National Institute for Research in Tuberculosis as Head, Division of Clinical Research.

SESSION VI: CASE STUDIES IN INNOVATIVE DRUG-RESISTANT TB CONTROL EFFORTS

Session Objectives:

- Discuss the use of mobile technology to track disease, train the TB workforce, and improve overall TB health care delivery.
- Present innovative methods or alternative development strategies to improve control and treatment of drug-resistant TB.

Session Chair:

- Janet Tobias, Mount Sinai School of Medicine

Leveraging Technology and Unique Development Models to Improve Access to Care and Compliance with Treatment Regimens

11:00-11:15 a.m. *Case Study: Mobile Technology to Improve Drug-Resistant TB Control and Care in Karachi*

AAMIR KHAN [by teleconference]
Indus Hospital, Pakistan

11:15-11:30 a.m. *Operation ASHA—Using Innovations and Biometrics to Prevent MDR TB and Provide a Social and Economic Return*

SHELLY BATRA
Operation ASHA, New Delhi

11:30-11:45 a.m. *MDR TB in Ethiopia: Failure of the International Response and How an NGO Filled the Gap*

ANNE GOLDFELD
Global Health Committee/Cambodian Health Committee
Harvard Medical School

11:45 a.m.-
12:15 p.m.

Discussion

12:15-1:15 p.m. Lunch

SESSION VII: DRUG SUPPLY CHAIN

Session Objectives:

- Present current methods of drug procurement in India, successes, and current challenges to effectively delivering quality-assured second-line drugs to patients.

Session Chairs:

- Iain Richardson, Eli Lilly & Co.
- Pradeep Saxena, Central TB Division, Directorate General of Health Services

1:15-1:30 p.m. ***Setting the Stage: Challenges in Drug Supply Chain Logistics***

PRASHANT YADAV
MIT-Zaragoza International Logistics Program

1:30-1:45 p.m. ***Implementation of India's National MDR TB Program***

PRADEEP SAXENA
RNTCP
Ministry of Health and Family Welfare

1:45-2:00 p.m. ***Potential for Impact in Second-Line TB Drug Pricing***

INDER SINGH
Clinton Health Access Initiative

2:00-2:15 p.m. ***Moving Towards a Functional Second-Line TB Drug Market***

OWEN ROBINSON
Partners In Health

2:15-2:45 p.m. ***Roundtable Discussion***

Facilitator: Anne Goldfeld, Global Health
Committee/Cambodian Health Committee, Harvard
Medical School

2:45-3:15 p.m. Tea Break

SESSION VIII: CLOSING PLENARY: THE INTERSECTION OF SCIENCE AND POLICY: CREATING A BLUEPRINT FOR ACTION

Session Objectives:

- Discuss potential policy approaches to address problems and gaps considered during the workshop.
- How can domestic programs and international partners work together to create a “blueprint for action” to address the problem of drug-resistant tuberculosis?
- Consider opportunities to address the problem of drug-resistant tuberculosis in India’s next 5-year budget plan.

Session Chairs:

- Elaine Gallin, QE Philanthropic Advisors
- Seyed E. Hasnain, Indian Institute of Technology

3:15-4:45 p.m.

Panelists:

- Kiran Katoch
- Prakash N. Tandon
- Gail Cassell
- Salmaan Keshavjee

Open Discussion with Workshop Participants

Appendix B

Summary of a Joint Meeting of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, and Indian Biomedical Research Agencies, Held April 20-21, 2011, New Delhi, India

On the two days following the workshop summarized in this volume, the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, held a forum in collaboration with the Indian Council of Medical Research (ICMR) and India's Departments of Health Research (DHR) and Biotechnology (DBT) entitled "Indo-NIAID Tuberculosis Drug Discovery Forum—Exploring Opportunities for Research Collaboration." The forum brought together scientists from the United States, Europe, and India to explore collaborative opportunities in TB drug discovery and development. Participants included researchers and administrators from government and university laboratories, not-for-profit product development organizations, and the pharmaceutical industry. The goals of the joint workshop were to:

- share the latest state-of-the-art scientific information on drug discovery research designed to help combat MDR and extensively drug-resistant (XDR) TB;
- summarize TB drug development projects of the pharmaceutical industry and the public sector currently under way;
- discuss TB drug development needs and ways in which biomedical research can contribute;
- identify partnership opportunities to advance and accelerate new drug discovery efforts so that therapeutic options for drug-resistant TB can be advanced and accelerated;

- explore potential connections for bioinformatics related to systems biology and the genomics of *Mycobacterium tuberculosis* (*M.tb.*); and
- discuss current gaps in translational research and how opportunities in the United States and India can be leveraged to help address these gaps.

At the conference, during a session convened by the Institute of Medicine (IOM), Barbara Laughon, NIAID; Gail Cassell, Harvard Medical School and Infectious Disease Research Institute; and several participants cited conclusions and recommendations emerging from the meeting that were especially important in the context of the recently completed workshop summarized herein.

DRUG SUSCEPTIBILITY ANALYSIS

- All countries affected by TB should conduct surveys to determine the strains of *M.tb.* prevalent in different regions and patterns of drug susceptibility. In India in particular, coordinated and systematic analysis of genomic variations in *M.tb.* across the country and across population groups should be performed.
- An important question is whether certain strains are more infectious and virulent. Drug-resistant strains may be more likely to spread rapidly and infect both children and adults.
- Genomic surveys should be accompanied by phenotypic screening and cohort studies to identify effective treatments and investigate how drug susceptibility patterns may change. This will be especially important to monitor as new classes of TB drugs are introduced. Such studies could contribute valuable information to lay the foundation for registration clinical trials of new anti-TB drugs.

THE RESEARCH INFRASTRUCTURE

- Important research ideas emerging from the conference could be supported by investigator-initiated research grants. NIAID, the lead agency supporting research on TB, has several program announcements for competitive research projects and welcomes applications.
- Research involving TB within India and between India and international partners is rich in opportunities and could draw on successful models in other disease areas of concern and other countries.
- Academic researchers and industrial drug developers in India may need to accelerate coordinated efforts to build on recent progress in combating drug-resistant TB.

- Meetings such as the workshop summarized in this volume and the Indo-NIAID forum create opportunities for collaboration.

DRUG DEVELOPMENT

- Translational efforts are needed to advance drug discovery candidates. These efforts should include examination of physiochemical properties, pharmacokinetics, efficacy, and formulations. Research resources for these activities are available within India. NIAID offers product development assistance for high-priority research areas such as TB.
- Evaluations of compounds against virulent *M.tb.* in animal models and in vitro are particularly promising, and NIAID can provide technical preclinical assistance in this area.
- Although it is a notable research challenge, new approaches to identifying and eliminating dormant mycobacteria are greatly needed and should be given high priority by the research community.
- Future workshops and forums for the exchange of information, along with collaborative efforts centered on anti-TB drug development, would be welcomed by Indian investigators and are recognized as critically important.

Appendix C

Participant Biographies

Shelly Batra, M.D., is President and Cofounder of Operation ASHA, a renowned senior obstetrician and gynecologist, an advanced laparoscopy surgeon, and a best-selling author in Delhi. Since 1991, she has been working tirelessly for slum dwellers in Delhi, not only by providing free consultations and counseling but also by operating on sick patients free of charge and organizing a team of specialists to help her in this work. She has also been involved with the Free Patient Department of Batra Hospital and Medical Research Center, which is run for the benefit of poor patients. Dr. Batra has worked pro bono for the dissemination of medical information with many television stations and newspapers and written two books for Penguin Publishers. She previously taught public health at the University of Chicago, Harris School of Public Policy, and has lectured at major Ivy League universities. With her medical background, she brings the experience necessary for running a health NGO. She is skilled at donor relations and fundraising and at representing Operation ASHA. Dr. Batra has been the recipient of multiple awards and recognitions, including the Exemplary Contribution Award for selfless work for the underserved, given by the Indian Medical Association.

Mercedes C. Becerra, Sc.D., is assistant professor in the Department of Global Health and Social Medicine at Harvard Medical School. She is a graduate of Harvard College (A.B. in history) and earned a doctor of science degree in epidemiology at the Harvard School of Public Health. Dr. Becerra's research focuses on the treatment of TB and the burden of this disease in patient households. She is the principal investigator of

a large ongoing study of the epidemiology of drug-resistant TB in Peru, which is supported by grants from the U.S. National Institutes of Health. She is also the recipient of a Charles H. Hood Foundation Child Health Research Award and is supported by a career development award from the U.S. National Heart, Lung, and Blood Institute. For more than 15 years, Dr. Becerra has worked with Partners In Health—an international non-profit organization that provides direct health care services and undertakes research and advocacy activities on behalf of those who are sick and living in poverty—helping to build and evaluate programs that treat patients with MDR TB.

Digambar Behera, M.D., is currently director of the LRS Institute of Tuberculosis and Respiratory Diseases in New Delhi. Formerly, he was professor in the Department of Pulmonary Medicine at the Postgraduate Institute of Medical Education and Research in Chandigarh. He completed his graduation from Sriram Chandra Bhanj Medical College in Cuttack in 1978 and post-graduation in medicine from the Postgraduate Institute of Medical Education and Research in Chandigarh in 1980. Dr. Behera has passed the National Board of Examinations in both General Medicine (1982) and Respiratory Medicine (1983). He received training at the University of Washington, Seattle, under the International Fogarty Fellowship awarded by NIH. Additionally, he received two International Cancer Research Exchange Technology Transfer Fellowships from the Union for International Cancer Control (UICC) to study lung cancer in Copenhagen, Denmark, and Sydney, Australia. Furthermore, he underwent training at the Memorial Sloan Kettering Cancer Center in New York. He has received 19 national and 7 international awards for his scientific contributions and has authored over 300 publications in national and international peer-reviewed journals. He is the author of six books, including one single-author two-volume textbook on pulmonary medicine, and is regarded as one of the foremost pulmonologists in India. Dr. Behera's current research interests include the epidemiology, diagnosis, and management of drug-resistant TB, lung cancer, smoking, pollution, and induced changes in airway.

Gail H. Cassell, Ph.D., is a visiting professor in the Department of Social Medicine, Harvard Medical School, and Vice President of TB Drug Discovery for the not-for-profit Infectious Disease Research Institute in Seattle. Dr. Cassell recently retired as vice president, scientific affairs, and distinguished Lilly research scholar for infectious diseases, Eli Lilly & Co., in Indianapolis, Indiana. In this capacity, among other things, she was responsible for initiating and leading the not-for-profit Lilly TB Drug Discovery Initiative, launched in 2007. In 2003, she was one of two individuals at Lilly who initiated and developed the Lilly Multidrug Resistant Tuberculosis Partner-

ship. The partnership has resulted in company support to date amounting to \$135 million and is the largest philanthropic effort in Lilly's 125-year history. The partnership now involves more than 20 partners, including WHO and CDC. Dr. Cassell is the former vice president of infectious diseases drug discovery and clinical development at Lilly, where she led the program for a hepatitis C protease inhibitor from the discovery phase to clinical candidate. The compound is now in phase III clinical trials under the direction of Vertex. Prior to joining Lilly in 1997, Dr. Cassell was Charles H. McCauley professor and chairman of the Department of Microbiology at the University of Alabama Schools of Medicine and Dentistry at Birmingham, a department that ranked first in research funding from NIH during the decade of her leadership. She obtained her B.S. from the University of Alabama in Tuscaloosa and in 1993 was selected by that institution as one of the top 31 female graduates of the 20th century. Dr. Cassell obtained her Ph.D. in microbiology from the University of Alabama at Birmingham and was selected as the university's 2003 Distinguished Alumnus.

Puneet K. Dewan, M.D., is medical officer, tuberculosis, with the WHO Regional Office for Southeast Asia. He is a graduate of the University of California, Los Angeles, and an internal medicine physician with the University of Washington, Seattle. He joined the U.S. CDC as an Epidemic Intelligence Service officer in 2001 in the Division of Tuberculosis Elimination. For more than 10 years, he has worked on TB control, from local program management and clinical care in San Francisco, to technical and policy analysis and advice for ministries of health in multiple countries, most notably India. Dr. Dewan is a recipient of the U.S. Public Health Service's Outstanding Service Medal, and he seeks to improve the quality and efficacy of TB control services in those countries with the highest TB burden.

Kunchok Dorjee, M.D., M.P.H., was born and raised in the Tibetan exile community in India. He completed high school at Tibetan Children's Village School in Dharamsala, India. His medical education was completed in 2004 at Indira Gandhi Medical College, Shimla, India. Dr. Dorjee has worked as a medical officer in the Delek Hospital in Dharamsala, the seat of the Tibetan Government in Exile. In 2008, he received the U.S. Government's Fulbright Scholarship Award. He completed his master of public health degree at Stony Brook University in New York in May 2010. In June 2010, he attended the Graduate Summer Institute of Epidemiology and Biostatistics at Johns Hopkins Bloomberg School of Public Health. Dr. Dorjee received the ICHORTA Scholarship Award to attend training in operational research on TB at Johns Hopkins Center for Tuberculosis Research. From

September 2010 to the present, he has been director of the Tibetan TB Control Programme, Delek Hospital, Tibetan Government in Exile in India.

Sébastien Gagneux, Ph.D., is unit head and assistant professor at the Swiss Tropical and Public Health Institute (Swiss TPH) and University of Basel, Switzerland. Dr. Gagneux received his Ph.D. from the University of Basel in 2001. Thereafter, he spent 4 years as a postdoctoral fellow at Stanford University and 2 years at the Institute for Systems Biology in Seattle. Before joining Swiss TPH in 2010, he spent 3 years as program leader at the Medical Research Council (MRC) National Institute for Medical Research in London, UK. Dr. Gagneux studies the causes and consequences of genetic diversity in *M.tb.* from a micro- and macroevolutionary perspective. The microevolutionary perspective comprises evaluating the effect of bacterial genetics and compensatory evolution on the reproductive fitness and transmission dynamics of drug-resistant *M.tb.* The macroevolutionary arm of his research focuses on the global biogeography and population genomics of *M.tb.* and on the effect of mycobacterial variation on host-pathogen interaction.

Elaine K. Gallin, Ph.D., is currently a partner at QE Philanthropic Advisors, a consulting firm established in 2010 that serves nonprofits specializing in biomedical research, science and math education, and international health. From 1999 through February 2010, Dr. Gallin served as the Doris Duke Charitable Foundation's (DDCF's) first program director for medical research. In that capacity, she led the creation and management of a portfolio of grant programs that committed more than \$185 million to supporting clinical research. Dr. Gallin also designed and led DDCF's \$65 million African Health Initiative. Launched in September 2007, this initiative supports large-scale health services delivery projects designed to provide integrated primary health care linked to rigorous operations and implementation research in several sub-Saharan African communities. Before joining DDCF, Dr. Gallin spent two decades working for the U.S. government, first as research physiologist and then as research administrator, last serving as deputy director of the Office of International Health Programs in the U.S. Department of Energy, overseeing health research programs in countries of the former Soviet Union. During this period, she also spent a sabbatical year working with the Science Committee of the U.S. House of Representatives as a congressional science fellow. Dr. Gallin has participated in numerous professional committees and review panels, including several for the IOM and NIH. She was a founding member and the first vice chair of the Health Research Alliance (an alliance of not-for-profit, nongovernmental research funders). She is currently a member of the Sickle Cell Disease Advisory Committee at the National Heart, Lung, and Blood Institute; the Forum on

Drug Discovery, Development, and Translation at the IOM; the Scientific Advisory Board for the Avon Foundation; and the President's Council of Cornell Women. Dr. Gallin received her B.S. from Cornell University, her Ph.D. from the City University of New York, and completed postdoctoral fellowships in physiology at Johns Hopkins University Medical School and Columbia University Medical School.

Anne Goldfeld, M.D., attended Brown University and the University of California, Berkeley, where she earned a bachelor's degree in zoology. After receiving her M.D. from Albert Einstein College of Medicine, she completed a residency in internal medicine and a clinical fellowship in infectious disease at Massachusetts General Hospital, followed by postdoctoral research training at Harvard University and the Dana-Farber Cancer Institute. Dr. Goldfeld has been a devoted advocate for health and human rights, particularly as related to refugees working in many postconflict settings around the world. In 1994, she cofounded the Global Health Committee/Cambodian Health Committee with Sok Thim. She has pioneered community-based TB treatment and more recently AIDS treatment strategies in southeastern Cambodia that integrate basic scientific discovery with operational models. Dr. Goldfeld is a senior investigator at Uganda's Infectious Diseases Institute (IDI), a professor of medicine at Harvard Medical School, and a physician in medicine in the Division of Infectious Disease at Brigham and Women's Hospital.

Seyed E. Hasnain, Ph.D., D.Sc., is professor at the School of Biological Sciences, Indian Institute of Technology, New Delhi. Dr. Hasnain's laboratory works on the molecular pathogenesis of infectious organisms and is designing novel intervention strategies, currently focused on the functional molecular infection epidemiology of *M.tb*. Studying the dissemination dynamics of *M.tb* isolates from India, using genetic typing, he showed the presence of ancestral isolates as the predominant form circulating in India, which could explain the lack of concordance between bacterial load and disease burden in the Indian population. Functional characterization of *M.tb* with the hypothetical PE/PPE protein family has demonstrated their importance as diagnostics, vaccine candidates, and drug targets. Dr. Hasnain has also contributed extensively to understanding of the transcriptional regulation and high-level expression of heterologous genes in the baculovirus insect cell system.

Kiran Katoch, M.D., M.B.B.S., is director of the National JALMA Institute for Leprosy and Other Mycobacterial Diseases, ICMR, in Agra, India. She also plans and coordinates the work of the Model Rural Health Research Unit in Ghatampur, Kanpur, which includes the epidemiology of various

diseases and other health-related issues. Dr. Katoch has 33 years of experience in medical research—29 years in leprosy and 12 years in TB, filariasis, and other health problems of the rural population. After completing her medical degree in 1979, Dr. Katoch joined what was then called the Central JALMA Institute for Leprosy. From 1979 to the present, she has held a number of positions at the institute, including research officer, senior research officer, assistant director and head of Medical Unit I, deputy director senior grade scientist and head of Medical Unit I, director-in-charge, and director (her current position). Dr. Katoch has produced more than 150 publications on leprosy, TB, and filariasis in various journals and has presented at more than 100 international and national conferences, workshops, and symposia. She has served as a member of various expert committees for national and international agencies, including WHO's Technical Advisory Group on Leprosy (2003–2005). Since the beginning of her career, Dr. Katoch has been working as a clinician/clinical researcher. Her work initially pertained to clinical and therapeutic research on leprosy and during recent years has grown to include TB in field settings such as Ghatampur. Dr. Katoch developed and evaluated several important regimens for the treatment of leprosy. She has contributed to a better understanding of the disease's effects on various body systems, as well evaluated the protective effect of vaccines against leprosy and TB. Dr. Katoch has played an active role in the establishment of epidemiological studies on leprosy, TB, and filariasis at Ghatampur. This program has been expanded and developed into a Model Rural Health Research Unit. As a clinician, Dr. Katoch has coordinated various studies through this Research Unit that use clinical, epidemiological (conventional as well as molecular), and other relevant modern technology tools to address various health issues. Her coordination of the Research Unit's programs goes beyond the main research focus on leprosy, TB, and filariasis to pursue the broader objective of bringing modern technology to the needy, especially deprived sections of society in rural settings.

Vishwa Mohan Katoch, M.D., is secretary to the Government of India, Department of Health Research, Ministry of Health and Family Welfare, and Director General, ICMR. His academic qualifications include an M.B.B.S from Himachal Pradesh University in Shimla and an M.D. from AIIMS in New Delhi. His research and teaching experience includes residencies at Safdarjung Hospital and AIIMS (1976–1978); fellow in the Tuberculosis Research Laboratory, Department of Veterans Affairs (VA) Medical Center, Long Beach, California (1980–1981); and National Institute for Medical Research, London (1984–1985). Other specialized training includes the ICMR for Talent Search Schemes (TSS) fellows and posts at JALMA in Agra in 1978. Dr. Katoch was selected as director of the national JALMA Insti-

tute for Leprosy and Other Mycobacterial Diseases in December 2001; as first secretary to the Government of India, Department of Health Research, Ministry of Health and Family Welfare; and as director general of ICMR in 2008. Dr. Katoch has developed molecular methods for rapid diagnosis of TB and leprosy, DNA chips, DNA fingerprinting methods, and viability determination methods such as ATP bioluminescence. He has contributed to 251 national and international research papers. Studies carried out by his research group and with collaborators from other institutes, universities, and medical colleges have led to important new findings and new technologies, such as enzyme-based methods in the 1980s, molecular biology-based techniques in the 1990s, and genomics-based methods in the recent past. These studies have resulted in the identification of new genotypes, new diagnostic techniques, and molecules for better understanding of the molecular basis of drug resistance and mechanisms of pathogenesis of TB, leprosy, and other mycobacterial infections. Dr. Katoch is the recipient of numerous awards, including the Young Scientist Award of the Indian Association of Medical Microbiologists (IAMM) (1985); the Shere-I-Kashmir Shiekh Abdulla Memorial Oration Award (1989); the Dr. C. G. S. Iyer Oration Award of ICMR (1990); the Erwin Stindl Memorial Oration Award of German Leprosy Relief Organization (1991); the Dr. S. C. Agarwal Oration Award of IAMM (1994); the Dr. Manu Patel Prize of the Indian Association of Dermatologists, Venereologists, and Leprologists (IADVL) (1999); and most recently, the JALMA Trust Fund Oration Award (1999) of ICMR, the IAMM Endowment Award (2003), the Ranbaxy Science Foundation Award (2004), and the Excellence in Science and Technology Award of the Indian Science Congress Association (2010–2011). Dr. Katoch is a fellow of a number of societies in India, including the National Academy of Sciences; the National Academy of Medical Sciences; the Academy of Sciences, Bangalore; and the Indian Academy of Science.

Salmaan Keshavjee, M.D., Ph.D., M.A., Sc.M., is assistant professor in the Department of Medicine and the Department of Global Health and Social Medicine (DGHSM) at Harvard Medical School. He is trained as a physician and a social anthropologist and is the director of the Program in Infectious Disease and Social Change at DGHSM. He is an associate physician at Brigham and Women's Hospital in the Division of Global Health Equity and senior TB specialist at Partners In Health (PIH). Dr. Keshavjee completed his thesis work on the anthropology of NGO health policies around pharmaceuticals in post-Soviet Tajikistan. His clinical research has focused on the implementation of drug-resistant TB treatment projects run by PIH and associated treatment outcomes. He has worked extensively with PIH's drug-resistant TB program in Russia since 2000. From 2006 to 2008, he was research director and deputy country director for the PIH Lesotho

Initiative, launching one of the first community-based treatment programs for MDR TB/HIV coinfection in sub-Saharan Africa. Since 2007, he has led PIH's Russia research initiative, coordinating a multidisciplinary team studying treatment outcomes in drug-resistant TB. This work is informing efforts to treat drug-resistant TB in the region, including Central Asia, and has resulted in several manuscripts of global clinical and policy significance. Since 2005, Dr. Keshavjee has represented PIH on the GLC for MDR TB, the principal global mechanism for MDR TB treatment expansion, housed at the STOP TB Partnership and WHO. From 2007 until September 2010, he served as the committee's chair. Through his roles at Harvard, PIH, and the GLC, Dr. Keshavjee has advised numerous national programs on the clinical and programmatic management of MDR TB.

Aamir Khan, M.D., Ph.D., is an epidemiologist based in Karachi, Pakistan. He trained in medicine at the Aga Khan University and in public health at The Johns Hopkins University, where he is associate faculty. He is the founder and executive director of IRD, a research enterprise committed to improving global health and development through the use of appropriate technologies. Dr. Khan also directs the Indus Hospital Research Center in Karachi. In addition to his work in Pakistan, he has led large-scale surveys and established research studies in Tajikistan, the United States, Ethiopia, Guatemala, Mexico, and Brazil over the past 15 years. Dr. Khan is cofounder of the Innovations in International Health (IIH) program, based at the D-Lab at Massachusetts Institute of Technology (MIT), and is a founding member of the openXdata.org consortium. He leads the End-User Requirements group on the Open Source Mobile Data Collection for Vaccine Trials (OMEVAC) and Mobile Innovations in Recording Child Vaccination and Health Data in Immunization Registers (mVAC) grants, based at the University of Bergen. IRD's in-house mobile phone system (Interactive Alerts for Childhood Pneumonia) was a winning entry in the Design Triennial at the Smithsonian Cooper-Hewitt National Design Museum in New York City. Dr. Khan serves on the STOP TB Partnership Working Group on MDR TB, based at WHO in Geneva, and helped draft Pakistan's successful \$173 million Global Fund application for scaling up MDR TB control.

Ashok Kumar has been public health specialist for Central Health Services (CHS), Government of India, since April 1980. Presently, he holds the posts of deputy director general and head, Central TB Division, and project director, RNTCP/Ministry of Health and Family Welfare, Government of India. Dr. Kumar has worked as Junior Medical Officer, WHO Global Smallpox Eradication (1975); field officer, ICMR, research on cholera (1976); teaching faculty for community medicine at the Institute of Medical Sciences

Varanasi and Maulana Azad Medical College, New Delhi (1977–1980); head, epidemiology, Statistics and Training Division of Central Leprosy Teaching and Research Institute (CLTRI), Chengalpattu (1980–1988); joint director and head, Division of Helminthology at National Institute of Communicable Diseases (NICD), Delhi; director, Guinea Worm Disease Eradication Programme (1988–1995); and assistant director general (TB and Mental Health), Government of India (1995–1996). He has held numerous positions over nearly four decades, including, most recently, deputy commissioner and Head, Maternal and Child Health (MCH) Division, Ministry of Health and Family Welfare, Government of India (1996–2000); director, National Anti Malaria (and Other Vector Borne Diseases) Programme of India (2000–2002); deputy director general and head, Central Leprosy Division, for the National Leprosy Eradication Programme (2002–2004); director, Central Bureau of Health Intelligence, Ministry of Health and Family Welfare, Government of India (2004–February 2011); and Head, WHO Collaborating Center for the Family of International Classifications, India (2008–2011). He has published more than 125 scientific papers in various national and international journals and has made valuable contributions to more than 300 conferences, seminars, symposia, and workshops at the national and international levels. Dr. Kumar has received numerous awards and honors, including the WHO and GOI Meritorious Service Certificate for Global Small Pox Eradication, WHO Fellowship (1985), Technical Focal Point SAARC TB Control in India, the Carter Cerner (USA) Award for Guinea Worm Disease Eradication, Meritorious Service Award for Leprosy Elimination, the Indian Association of Epidemiologists Award for Guinea Worm Disease Eradication from India, the Dr. B. C. Das Gupta Oration Award of the Indian Public Health Association (IPHA), and the Golden Jubilee Award of IPHA. He has served as a member of the Central Council of the Family of International Classifications Network, WHO (2008 to present); president of the Association of Public Health Specialists of CHS; national president of IPHA; member of the WHO Special Programme for Research and Training in Tropical Diseases (TDR) Steering Committee on Implementation Research (2001–2003); member of the WHO Technical Advisory Group on Global Elimination of Lymphatic Filariasis; member of the WHO Expert Advisory Panel on Parasitic Diseases; member of the WHO Global Epidemiology Network; elected fellow of IPHA; elected fellow of the Indian Society for Malaria and Other Communicable Diseases; and life member of the Indian Association of Leprologists. In his advisory capacities, Dr. Kumar has visited 29 countries in the Americas, Europe, Asia, Africa, and the Mediterranean region.

S. Siva Kumar is technical assistant (research) in the Immunology Department of the National Institute for Research in Tuberculosis, Chennai (for-

merly the Tuberculosis Research Centre), ICMR. His area of research is the molecular epidemiology of *M.tb*. He has coauthored two papers on the subject, addressing drug resistance among different genotypes of *M.tb*. isolated from patients in Tiruvallur, South India, and the impact of HIV infection on the recurrence of TB in South India.

Krishan Lal, M.Sc., Ph.D., served as lecturer and joined the National Physical Laboratory, New Delhi, and rose to be director. His research and development contributions are in crystal growth and lattice imperfections and instrumentation, certified reference materials, and data for materials. He has made significant contributions in research and development, scientific leadership, and the development of international collaboration. His work has led to a deeper understanding of the nature of real materials and their interaction with radiation and external fields. Dr. Lal is president, INSA, and formerly served as president, CODATA (2006–2010); editor, *Zeits für Kristall*; and vice president, Asia-Pacific Academy of Materials. He is the recipient of the Professor S. K. Mitra Birth Centenary Gold Medal of the Indian Science Congress Association and the Jawaharlal Nehru Birth Centenary Visiting Fellowship, and delivered the D. S. Kothari Memorial Lecture. Dr. Lal has been IBM India fellow; visiting professor, University of Tokyo and Tech. University, Darmstadt; honorary professor, Indian Institute of Technology (IIT), Kanpur; visiting professor, Punjab University, Chandigarh; visiting professor, IIT Delhi; and adjunct professor, IIT Kharagpur. He has edited 9 books, has published 22 invited papers and more than 100 research papers, and holds 7 patents.

Edward A. Nardell, M.D., is a pulmonologist with a special interest in TB. He trained in pulmonary medicine at Massachusetts General Hospital, with additional research training at Boston University School of Medicine. While at Boston City Hospital, he became director of TB control for the city of Boston. In 1981, he became chief of pulmonary medicine and director of TB control for the city of Cambridge, Massachusetts, positions he held until 2005. His principal academic appointment is as associate professor of medicine, Harvard Medical School, with secondary parallel appointments in the Department of Social Medicine and Harvard School of Public Health. In the early 1980s, Dr. Nardell became medical director of TB control for the Massachusetts Department of Public Health, a position he held for 18 years. In 2002, he joined PIH as director of TB research. In 2005, he left Cambridge Hospital to assume a full-time research position in the Department of Social Medicine and Health Inequalities, Brigham and Women's Hospital, the hospital arm of PIH. He is also a member of the Pulmonary Division at Brigham and Women's Hospital, where he serves on the pulmonary consult service. Dr. Nardell's research interests include the control

of MDR TB in Peru, Russia, and other high-burden countries. His special research interest is airborne TB transmission and control. He currently has a project in South Africa, funded by the National Institute of Occupational Safety and Health (NIOSH), studying the transmission of MDR TB using large numbers of guinea pigs to quantify the infectiousness of MDR TB patients and the effectiveness of various control interventions, including ultraviolet germicidal irradiation. Dr. Nardell is past president of the Massachusetts Thoracic Society and the North American Region, International Union Against Tuberculosis and Lung Disease. He was the 2005 recipient of the Chadwick Medal of the Massachusetts Thoracic Society.

Neeraj Raizada, M.D., M.P.H., is a medical officer with the Foundation for Innovative New Diagnostics (FIND). He joined FIND in 2008. Dr. Raizada completed his medical studies at the Moscow Medical Academy in 1997. Following this, he undertook clinical practice and has worked in a large number of institutions in Delhi. From 2001, he was associated with M. P. Shah Medical College, Gujarat, India, where he earned his postgraduate degree in public health and also worked as lecturer. His thesis focused on stigma and discrimination faced by people living with HIV/AIDS. He also undertook a number of other studies focusing on various aspects of this disease. In 2004, Dr. Raizada worked as a consultant in TB/HIV coinfection, joining India's RNTCP at the Central TB Division. There he worked closely with the country program manager, focusing on establishing systems to improve access to care for TB patients coinfecting with HIV. During his association with the Central TB Division, he actively contributed to the development of the national training modules for TB/HIV, organizing and facilitating training of trainers on TB/HIV across the country, conducting HIV surveillance in TB patients, and developing the national framework for joint TB/HIV collaborative activities as well as a number of new pilot initiatives in TB/HIV.

K. Srinath Reddy, M.D., M.Sc., as president of the Public Health Foundation of India, is playing a major role in strengthening training, research, and policy development in the area of public health in India. Formerly head of the Department of Cardiology at AIIMS, Dr. Reddy is a leading international authority in preventive cardiology. He has worked to promote cardiovascular health, tobacco control, chronic disease prevention, and healthy living across the life span. Dr. Reddy has served on many WHO expert panels and chairs the Science and Policy Initiatives Committee of the World Heart Federation. He is presently chairing the High Level Expert Group constituted by the Government of India to develop a framework for universal health care coverage in India. Dr. Reddy chairs the Core Advisory Group on Health and Human Rights for the National Human Rights Com-

mission of India and is also a member of the National Science and Engineering Research Board of the Government of India. Recently appointed the first Bernard Lown visiting professor of cardiovascular health at the Harvard School of Public Health, Dr. Reddy is also an adjunct professor of the Rollins School of Public Health, Emory University.

Iain Richardson, M.Ch.E., is a graduate in chemical engineering from the University of Edinburgh with a master's degree in biochemical engineering from University College London. He has worked for Eli Lilly & Co. for more than 20 years in the Manufacturing Division. A native of Scotland, he joined Lilly at its Liverpool facility in Technical Services before relocating to the United States in 1991. During 9 years in the United States, Mr. Richardson held leadership positions in the company's Animal Health division before becoming director of manufacturing strategy in 1998. In 2000, he moved to Geneva, Switzerland, where he had manufacturing responsibility for Contract Manufacturing operations in Europe, the Middle East, Africa, and Lilly Contract Manufacturing operations in the Asia-Pacific area. It was in this assignment that he first began working on Lilly's MDR TB philanthropic initiative, with particular responsibility for the transfer of technology for cycloserine and capreomycin to the identified manufacturing partners. Mr. Richardson relocated back to the United States in 2006. Since then he has been responsible for Lilly's Contract Manufacturing processes globally and is now responsible for Global Supply Chain and Logistics operations for the company. He continues to lead Lilly's transfer of technology and product supply initiatives for the MDR TB program.

Owen Robinson, M.P.P., is partnerships manager for the Mirebalais National Teaching Hospital, a 320-bed public referral center being built by Partners In Health in central Haiti. Prior to joining PIH, he spent 3 years as manager of New Initiatives at the Clinton Health Access Initiative (CHAI), where his work focused on global access barriers to quality TB medicines and other essential health commodities. Mr. Robinson has also served as a consultant and project manager in the health care sector for the Boston Consulting Group (BCG). He holds an A.B. degree from Harvard University and a master's degree in public policy from Harvard's Kennedy School of Government.

Camilla Rodrigues, M.B.B.S., M.D., is consultant clinical microbiologist and chair of infection control at the Hinduja Hospital. She completed her M.B.B.S. from Armed Forces Medical College (AFMC) in Pune, India, in 1979, and subsequently served a 5-year Short Service Commission in the Indian Navy as a medical officer. She completed her M.D. (microbiology) from AFMC in 1987 and joined the Hinduja Hospital in 1988. She

is currently a recognized postgraduate teacher for Diplomate of National Board, microbiology and an M.Sc. and Ph.D. guide at the University of Mumbai. She served under the Directorate General of Health Services as a member of the task force to assess, review, and suggest measures for antibiotic resistance. She is currently a member of the National Working Group for Tuberculosis on Case Finding and Diagnostics for the National Strategic Plan (2012–2017), Central TB Division, and a member of the National Laboratory Committee (NLC) under the RNTCP. Dr. Rodrigues has authored 162 publications in international and national journals, as well as book chapters, and conducted 68 research projects as the principal or coinvestigator, with TB as a focus of her research. She has received 16 awards/prizes and given more than 400 presentations internationally and regionally.

Dr. Kuldeep Singh Sachdeva is chief medical officer, Central TB Division, Ministry of Health and Family Welfare, Government of India. He holds a bachelor's degree in medicine and surgery from Maulana Azad College, University of Delhi, along with a diploma in TB and chest diseases from V.P. Chest Institute and an M.B.A. in health care administration from the Faculty of Management Studies, University of Delhi. Dr. Sachdeva has held several senior positions within the Ministry of Health. Prior to working with the Central TB Division, he was chief medical officer, Essential Drugs Programme, Central Procurement Agency (2004–2006); chief medical officer, Department of Medicine, Lok Nayak Hospital, New Delhi (1989–2003); and zonal coordinator for various public health programs for Delhi (1994–2002), including the Pulse Polio Immunization Programme and the Cancer Control Programme. In his current position as chief medical officer, Central TB Division, Dr. Singh is team leader and nodal officer for programmatic management of drug-resistant TB; diagnostics, including quality assurance of laboratories and laboratory scale-up for newer diagnostics; public–private mix in TB control and advocacy; communication and social mobilization; and health system strengthening for TB control, among other responsibilities. He is also a member of the governing board of the South Asian Association for Regional Cooperation (SAARC) TB/HIV Centre. In addition, Dr. Sachdeva is a WHO fellow in drug and alcohol medicine from New South Wales Institute of Psychiatry, Sydney, Australia. He has also been a member of a monitoring and evaluation mission for the STOP TB Partnership Challenge Facility, India. Dr. Sachdeva has been a contributor to numerous reports and academic papers.

Rohit Sarin, M.D., DTCD, FNCCP, is a senior TB consultant with more than two decades of experience in this specialization and with specialized training in TB both within India and at the international level in Japan and

New York. At present, Dr. Sarin is a senior consultant at the LRS Institute of Tuberculosis and Respiratory Diseases. He is a postgraduate teacher for Diplomate of National Board, Students of Respiratory Diseases, and is a national trainer for the RNTCP. Under his leadership, more than 10,000 trainers at the national and international levels have been trained in TB control. Dr. Sarin has produced numerous publications in national and international journals and has contributed to many books on TB. Because of his extensive experience, he is one of the editors of the *Indian Journal of Tuberculosis* and serves on the editorial board of the *Indian Journal of Chest Diseases* and the *Journal of Delhi TB Association*. Dr. Sarin also worked as WHO national consultant for more than 3 years and was instrumental in framing and pilot testing the RNTCP. He has also served as a temporary adviser of WHO on various aspects of TB control in the Southeast Asian Region. He is a member of the World TB Team and has been identified as a global resource for drug-resistant TB. He is a SAARC trainer for MDR TB and DOTS-Plus. Dr. Sarin has been a member of the International Joint Monitoring Mission for the RNTCP and a national RNTCP appraiser for states. He serves on the National DOTS-Plus Committee for MDR TB, the National Committee for Airborne Infection Control, the National Committee for Paediatric Guidelines, and the National Drug Monitoring Committee. He is one of the key people responsible for initiating private-sector involvement in the RNTCP and organized a workshop for the drafting of national policy in this area. He is a national facilitator for training of trainers in DOTS-Plus. He is also a member of the National Core Committee for promoting research under the RNTCP. In view of his outstanding contributions to the cause of fighting TB, the TB Association of India awarded Dr. Sarin the Commendation Certificate and Trophy in 1996. He is also the recipient of the R. Krishna Memorial Prize, the Dr. O. A. Sarma Award, and the Dr. K. C. Mohanty Award. He currently is vice chairman of the TB Association of India.

Pradeep Saxena, M.B.B.S., M.D., is director, Central Bureau of Health Intelligence, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, and head, WHO Collaborating Center for the Family of International Classifications, India. Dr. Saxena has worked in the Central Health Service, Ministry of Health and Family Welfare, Government of India, since 1987. He worked at the Central TB Division from 2003 to 2011 until his current post with the Central Bureau of Health Intelligence in New Delhi. Dr. Saxena has authored and presented a number of papers and book chapters on TB and drug logistics management. He served as member secretary of the technical committees, constituted by the Directorate General of Health Services, which finalized

the guidelines for storage of second-line anti-TB drugs to treat MDR TB and also the technical specifications of drugs used for treatment of XDR TB under the RNTCP. Dr. Saxena assisted in the development of strategy for supervision and monitoring of the RNTCP in India as well the revision of technical and operational guidelines for implementation of the RNTCP. He facilitated procurement and logistics management of first- and second-line anti-TB drugs and other medical materials under the RNTCP for various consignees in India. Dr. Saxena has revised training material on procurement and drug logistics management for different categories of RNTCP personnel, formulated annual training plans on procurement and drug logistics management, and organized and conducted various training programs in these areas for RNTCP personnel across the country. He is actively associated with the formulation of project implementation plans for RNTCP Phase-II programs through World Bank and Global Fund support. Dr. Saxena served as a member of the central appraisal team from India's Central TB Division, which visited many states from 2003 to 2006 to evaluate their preparedness to implement RNTCP. He has also participated in a 2009 joint monitoring mission with WHO, World Bank, Global Fund, USAID, the United Kingdom's Department for International Development (DFID), and others, to review RNTCP performance.

Dr. Nagamiah Selvakumar is Scientist G at the National Institute for Research in Tuberculosis (formerly the Tuberculosis Research Centre), ICMR, Chennai, India. He graduated from Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Pondicherry, and earned a doctoral degree from Annamalai University. His research focuses on the bacteriology of pulmonary and extrapulmonary TB, sputum (acid-fast bacilli) microscopy, and molecular analysis of drug-resistant genes of *M.tb*. Dr. Selvakumar has been principal investigator for many national and WHO-funded projects. He served as a regional consultant (mycobacteriology) to the International Union Against Tuberculosis and Lung Disease and is a short-term consultant to WHO's Southeast Asian Region. The Tuberculosis Association of India honored him with a Dr. P. K. Sen Gold Medal Oration award. Dr. Selvakumar has produced more than 85 publications and attended more than 120 national and international events. He has served for 32 years in the Department of Bacteriology, National Institute for Research in Tuberculosis, Chennai. He has served as a laboratory consultant with the National Tuberculosis Programme, India, for more than a decade.

Dr. S. K. Sharma is chair of the Department of Medicine at AIIMS, New Delhi. He has made outstanding research contributions in the area of pulmonary medicine for the last three decades. His seminal contributions

in the field of TB, sarcoidosis, bronchial asthma, and obstructive sleep apnea are internationally recognized. He has published 309 papers in various national and international journals. In the capacity of chair of the National Task Force on the Involvement of Medical Colleges in the TB Control Programme of India (2002–2011), he has been responsible for the implementation of DOTS in all of India's medical colleges. Dr. Sharma has edited several books (*Tuberculosis*; two volumes of *Advances in Respiratory Medicine*, first edition [2008]; and the second edition [in press] of *Davidson's Clinical Cases in Medicine*, the first edition of which was awarded First Prize of the British Medical Association in 2009). He has received numerous awards: four ICMR awards, including the Basanti Devi Amir Chand Award; the Saroj-Jyoti Award (twice); the Hari Om Ashram Alembic Award; the Ranbaxy Research Award; the Lupin Chest Orator Award; the Rabindranath Tagore Orator; the Searle Orator; the Dr. Devi Chand Memorial Gold Medal Orator; and the VR Joshi JAPI Award for Outstanding Referee. Dr. Sharma is editor of the *Indian Journal of Chest Diseases and Allied Sciences*, executive editor and section editor of the pulmonology section of *A.P.I. Textbook of Medicine* (ninth edition), section editor of the *Textbook on Clinical Pharmacology*, associate editor of the *Indian Journal of Tuberculosis*, and editorial board member of *Chest*. He is an expert member of several task forces in ICMR; the Department of Biotechnology, Ministry of Science and Technology; the Ministry of Health and Family Welfare; and the National Institute of Immunology. He is chair of several committees in the Ministry of Health and Family Welfare. He has been the recipient of various fellowships and is an elected member of the Faculty Council of the Indian College of Physicians.

Thomas M. Shinnick, Ph.D., is associate director for global laboratory activities, Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, U.S. CDC. Dr. Shinnick is adjunct professor, Department of Microbiology and Immunology, Emory University. He received a B.S. from the University of Wisconsin-Madison, and a Ph.D. (biochemistry) from MIT. He also underwent postdoctoral training at the Research Institute of Scripps Clinic. His honors include a Johnson & Johnson Pre-doctoral Fellowship; a Helen Hay Whitney Foundation Postdoctoral Fellowship; the Arthur S. Flemming Award; fellow, American Academy of Microbiology; and Senior Biomedical Research Service. His national activities include serving as chairman, Division U, American Society for Microbiology; National Tuberculosis Task Force member; and member of the Scientific Advisory Board for the Heiser Program. International activities include serving on the Steering Committee of the Global Laboratory Initiative (GLI) Work Group of the STOP TB Partnership; the WHO STOP TB Working Group on Diagnostics; the WHO Supranational

Laboratory Network; and the Steering Committee for the WHO/TDR TB strain bank. Dr. Shinnicks's editorial activities include associate editor of the *International Journal of Tuberculosis and Lung Diseases* and the editorial board of *Emerging Infectious Diseases*, *Tuberculosis*, and *Current Microbiology*. His scientific interests include understanding the biology and genetics of the pathogenic mycobacteria, elucidating mechanisms of the pathogenicity and drug resistance of *M.tb.*, developing rapid methods for the diagnosis of mycobacterial infections, and using genotyping to support TB control programs and elucidate the dynamics of transmission. Dr. Shinnick has authored/coauthored more than 150 publications in addition to serving as the editor of one book.

Inder Singh, M.B.A., M.P.P., S.M., is executive vice president of access programs at CHAI. He oversees a group of 40 business professionals and scientists and a portfolio of initiatives designed to enable greater access to medicines and diagnostics. He and his team have negotiated a series of agreements with pharmaceutical companies that have lowered the price of drugs for HIV/AIDS, malaria, and TB by up to 80 percent for 74 developing country governments, WHO, and the Global Fund, leading to more than \$1 billion in cost savings. Prior to joining CHAI, Mr. Singh worked in consulting and at a series of start-up companies in the information technology and medical industries. He is also the founder of a successful nonprofit organization that supports children undergoing extensive physical rehabilitation. Mr. Singh is a magna cum laude graduate of the University of Michigan School of Engineering and holds graduate degrees in business administration, public policy, and biomedical enterprise from MIT's Sloan School of Management, Harvard's Kennedy School of Government, and the Harvard-MIT Division of Health Science and Technology, respectively.

Sarman Singh, M.D., is professor and head of the Division of Clinical Microbiology at AIIMS, India's premier medical institution. He graduated in medicine from King George's Medical College, Lucknow, India, and earned an M.D. from the Post Graduate Institute of Medical Education and Research, Chandigarh, India. He was also trained in the epidemiology of infectious diseases at the School of Epidemiology, University of Michigan. Dr. Singh has received several national and international awards for his original contributions in the field of diagnosis of TB and leishmaniasis. He holds seven patents and has produced more than 200 publications in peer-reviewed journals/proceedings. He is principal investigator of more than 12 research projects, mainly on TB and leishmaniasis, funded by ICMR, the Australia-India Council, and the U.S. National Institutes of Health. For more than 20 years, the focus of Dr. Singh's research has been on developing better diagnostic tools for infectious diseases, particularly MDR/XDR

TB in HIV-infected and HIV-uninfected patients. He has presented his work across the globe. He has also organized three international conferences on opportunistic pathogens in AIDS.

Soumya Swaminathan, M.D., is a pediatrician by training, having completed her medical education at the Armed Forces Medical College and AIIMS in India, followed by a fellowship in pediatric pulmonology at the Children's Hospital of Los Angeles. She has worked at the National Institute for Research in Tuberculosis (formerly the Tuberculosis Research Centre), Chennai, since 1992, where she served as principal investigator for several clinical trials investigating the treatment and prevention of TB among HIV-infected patients. She has directed HIV-related operational, epidemiologic, and behavioral research. Dr. Swaminathan heads the Division of Clinical Research at the center and is the co-principal investigator for the NIH International Centers for Excellence in Research. She has produced more than 140 peer-reviewed publications and serves on many national and international committees. Her major research interests are in pediatric and adult TB, their interaction with HIV, and nutrition and management of coinfections, as well as pharmacokinetics and pharmacogenetics. Dr. Swaminathan served as coordinator for neglected priorities research at WHO/Special Programme for Research and Training in Tropical Diseases (TDR) for two years, overseeing a diverse research portfolio encompassing TB/HIV, malaria, onchocerciasis, visceral leishmaniasis, and other neglected tropical diseases. She is currently chair of the HIV section of the International Union Against TB and Lung Disease and a member of the TB steering committee of the IMPAACT network.

Prakash N. Tandon, M.B.B.S., M.S., is a neurosurgeon who has conducted internationally acclaimed scientific research and has played a critical role in the comprehensive development of neurosciences in India. Professor Tandon received his medical education at K. G. Medical College (now University), Lucknow, and an M.S. degree from Lucknow University. He received speciality training in neurosurgery and allied neurosciences at the Ullevål Hospital, Oslo University, Norway (1957-1958), and the Montreal Neurological Institute, McGill University, Canada. Declining several rewarding offers abroad, he returned to India to start the first Neurosurgical Service at his alma mater in 1961. In 1965, he was appointed professor and founded the Department of Neurosurgery at AIIMS. He catalyzed the establishment of the National Brain Research Centre (NBRC) at Manesar, for which he has been founder president. Professor Tandon's major research efforts deal primarily with neurological disorders of the nervous system of national relevance. This work has resulted in 250 scientific papers, more than a dozen

monographs, and a number of chapters in national and international textbooks. Professor Tandon is the coeditor of the *Textbook of Neurosurgery* and consulting editor of the *Textbook of Operative Neurosurgery*. He has been president of the Neurology Society of India; the National Academy of Sciences, India; the Indian National Science Academy; and the Indian Academy of Neurosciences. He has served as a member of the Governing Body of the Council of Scientific and Industrial Research, ICMR, and the Indian Council of Social Science Research (ICSSR). He has been chairman of the Central Drug Research Institute, Centre for Cellular and Molecular Biology, and the National Brain Research Centre. He was the founder and Co-chairman of the InterAcademy Panel (IAP) of The World Science Academies, a member of the International Council of Scientific Unions, Indo-U.S. Vaccine Action Programme (VAP), and Indo-U.S. Science and Technology (S&T) Forum (Governing Body). He was elected Fellow of the National Academy of Medical Sciences (1973) and served on its Council and as Vice President. He was elected a member of the Norwegian Academy of Sciences (1987) and honorary member of the Society of Neurological Surgeons, United States (1987). He was a foreign member of the Royal Society of Medicine, London (1992); member of the American Association of Advancement of Science, United States (2002); and honorary life member of the Indian Institute of Advanced Study, Shimla (2002). Currently he is emeritus professor at AIIMS, National Academy of Medical Sciences, and president of the National Brain Research Centre. Awards and honors received by Professor Tandon include Padma Sri (1973); Hon. Surgeon to the President of India (1977–1980); B. C. Roy Award for Developing a Speciality (1980); M. N. Sen Oration, ICMR (1980); University Grants Commission, National Lecturer (1982); Federation of Indian Chamber of Commerce and Industry Award for Life Sciences (1983); Jawaharlal Nehru Fellowship (1984–1985); member, Science Advisory Council to the Prime Minister (1986–1989); Dhanwantari Prize, INSA (1986); Outstanding Alumnus Award, K. G. Medical College, Lucknow (1987); O. P. Bhasin Award for Medical and Health Sciences (1988); Padma Bhushan (1989); S. S. Bhatnagar Fellowship (1990–1995); Basanti Devi Amir Chand Prize, ICMR (1991); B. C. Roy Award for Eminent Medical Scientist (1993); Sir C. V. Raman Medal of INSA (1997); D.Sc. (h.c., BHU); G. M. Modi Award for Innovative Science (1998); INDO-ASEAN Eminent Persons Lecturer (1999); M. N. Shah distinguished fellow (2000–2005); Firodia Award for Excellence in Science and Technology (2003); New Millennium Plaque of Honour in Medicine and Physiology (Indian Science Congress, 2002–2003); Professor Bachhawat Lifetime Achievement Award (Indian Academy of Neuroscience, 2003); National Academy of Sciences, India, President's Gold Medal (2006); and the Padma Vibhushan Award (2006).

Aleyamma Thomas, M.B.B.S., M.D., is Scientist G and Director-in-Charge, National Institute for Research in Tuberculosis, Chennai (formerly the Tuberculosis Research Centre). Dr. Thomas joined the institute in 1977 and has held positions of increasing responsibility from that time. She has experience conducting controlled clinical trials in TB and leprosy, as well as operational research on key aspects of the RNTCP. She is involved in organizing and conducting training on various aspects of TB control at the national, regional, and international levels and teaches undergraduate and postgraduate students from various medical colleges who are posted at the National Institute for Research in Tuberculosis. Dr. Thomas has more than 30 publications in national and international TB and leprosy journals.

Janet Tobias is a media/technology executive and an Emmy Award-winning director/producer with 20 years of experience working for three American networks—PBS, Discovery, and MSNBC. Ms. Tobias started her career with *60 Minutes* as Diane Sawyer's associate producer, where she distinguished herself working on a wide range of domestic and international stories. Ms. Tobias then moved with Ms. Sawyer to ABC News to launch *Prime Time Live*, where she produced/directed both domestic and international stories. Subsequently, she served as a national producer for *Dateline NBC* and also continued to produce and direct her own stories. Moving to VNI (which became New York Times Television) as an executive producer, she supervised the production of a foreign news show and reporting on a variety of foreign stories. Ms. Tobias then returned to ABC News to head editorial activities at its newly created Law and Justice Unit. In 1998, she began working as an executive with PBS. She continued her directing and writing career, winning two American Bar Association silver gavels. In 2001, she launched *LIFE 360*, a weekly PBS series. In 2002, Ms. Tobias joined Sawyer Media Systems, a creator of video technology for the web. She also continued to be involved in documentary production through her own company, Sierra/Tango Productions. In 2004, she was a founding partner of Ikana Media, a digital strategy and production company whose primary focus is on health care information. Over the past 5 years she has worked with a variety of clients in the health care arena on subjects ranging from broad-based delivery of health care information to communications efforts around obesity and HIV/AIDS. Ms. Tobias has received a number of additional awards, including two Cine Golden Eagles, two Casey medals for meritorious journalism, a National Headliner award, and a Sigma Delta Chi award. She is a member of the Writers Guild of America and a graduate of Yale University. She serves on several boards. She served from January to September 2009 as a senior fellow at the University of British Columbia, Sauder School of Business Centre for Sustainability and Social Innovation. In 2009, she was appointed to the Forum on Drug Discovery,

Development, and Translation of the IOM. In 2010, Ms. Tobias became an adjunct assistant professor of medicine in the Department of Health Evidence and Policy at Mount Sinai School of Medicine.

Prashant Yadav, M.B.A., Ph.D., is Senior Research Fellow and Director of Healthcare Research at the University of Michigan's William Davidson Institute and also serves on the faculty at the university's Ross School of Business and the School of Public Health. He is co-chair of the Procurement and Supply Chain Management Working Group of the Roll Back Malaria Partnership. Previously, Dr. Yadav was professor of supply chain management at the MIT-Zaragoza International Logistics Program, where he started a high-impact group focused on global health supply chains, and was a research affiliate at the MIT Center for Transportation and Logistics. Dr. Yadav's research explores the functioning of pharmaceutical supply chains in developing countries using a combination of empirical, analytical, and qualitative approaches. He is the author of many scientific publications in this area, and his work has been featured in prominent print and broadcast media. Dr. Yadav obtained his bachelor of engineering degree from the Indian Institute of Technology, his M.B.A. from the FORE School of Management, and his Ph.D. from the University of Alabama. Before entering academia, he worked for many years in the area of pharmaceutical strategy, analytics, and supply chain consulting.

