The Global Crisis of Drug-Resistant Tuberculosis and Leadership of China and the BRICS: Challenges and Opportunities: Summary of a Joint Workshop by the Institute of Medicine and the Institute of Microbiology, Chinese Academy of Sciences

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Steve Olson, Rebecca A. English, and Anne B. Claiborne, Rapporteurs; Forum on Drug Discovery, Development, and Translation; Board on Health Sciences Policy; Institute of Medicine

The Global Crisis of Drug-Resistant Tuberculosis and Leadership of China and the BRICS

Challenges and Opportunities

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by the Institute of Medicine and
the Institute of Microbiology, Chinese Academy of Sciences

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

Forum on Drug Discovery, Development, and Translation

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Willing is not enough; we must do."
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This workshop summary 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 workshop summary as sound as possible and to ensure that the workshop summary meets institutional standards for objectivity, evidence, and responsiveness to the study 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 workshop summary:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop

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Acronyms

AFB	acid-fast bacilli
AIDS	acquired immune deficiency syndrome
AMFm	Affordable Medicines Facility for Malaria
API	active pharmaceutical ingredient
ART	antiretroviral treatment
BLF	bronchoalveolar lavage fluid
BMGF	Bill & Melinda Gates Foundation
BMI	body mass index
BRICS	Brazil, Russia, India, China, and South Africa
CAMELIA	Cambodian Early versus Late Introduction of Antiretrovirals
China CDC	Chinese Center for Disease Control and Prevention
CIPRA	Comprehensive International Program for Research on AIDS
DNA	deoxyribonucleic acid
DOT	directly observed treatment
DOTS	Directly Observed Treatment-Short course
DR TB	drug-resistant tuberculosis
DST	drug susceptibility testing
EMR	electronic medical record
FLD	first-line anti-tuberculosis drug

GDF	Global Drug Facility
GHC	Global Health Committee
GLC	Green Light Committee
H3 Africa	Human Heredity and Health in Africa
HBC	high tuberculosis burden country
HIV	human immunodeficiency virus
IMCAS	Institute of Microbiology, Chinese Academy of Sciences
IOM	Institute of Medicine
IUATLD	International Union Against Tuberculosis and Lung Disease ("The Union")
K-RITH	KwaZulu-Natal Research Institute for Tuberculosis and HIV
LAMP	loop-mediated isothermal amplification
LED	light-emitting diode
LPA	line probe assay
MDR TB	multidrug-resistant tuberculosis
MHC	major histocompatibility complex
M.tb.	*Mycobacterium tuberculosis*
NGO	nongovernmental organization
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NTM	nontuberculous mycobacteria
PAS	para-aminosalicylic acid
PATRIC	Pathosystems Resource Integration Center
PCR	polymerase chain reaction
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PMDRT	programmatic treatment and management of MDR and XDR TB patients
PQR	Price and Quality Reporting
QFT	QuantiFERON-TB test
RIF	rifampicin
RNA	ribonucleic acid
RNTCP	Revised National TB Control Program
rRNA	ribosomal ribonucleic acid

SAT	simultaneous amplification test
SLD	second-line anti-tuberculosis drug
TB	tuberculosis
TBM	tuberculous meningitis
TDR TB	totally drug-resistant tuberculosis
THINK	Tuberculosis and HIV Investigative Network of KwaZulu-Natal
TST	tuberculin skin test
UNICEF	United Nations Children's Fund
U.S. CDC	U.S. Centers for Disease Control and Prevention
UV	ultraviolet
UVGI	ultraviolet germicidal irradiation
VNTR	variable-number tandem-repeat
WHO	World Health Organization
XDR TB	extensively drug-resistant tuberculosis

1

Introduction and Overview of the Workshop[1]

Since 2008, the Forum on Drug Discovery, Development, and Translation ("the Forum") of the Institute of Medicine (IOM) has hosted or co-hosted six domestic and international workshops addressing the global crisis of drug-resistant (DR) tuberculosis (TB). The first, held in Washington, DC, on November 5, 2008, built on a white paper commissioned by the Forum and authored by Keshavjee and Seung (2008) to examine seven broad issues (IOM, 2009):

1. Limitations of global TB estimates
2. The role of HIV infection in the spread of multidrug-resistant tuberculosis (MDR TB)
3. The importance of infection and transmission control
4. Problems associated with limited diagnostic capacity
5. Low rates of treatment
6. Bottlenecks in the procurement and distribution of quality-assured drugs
7. The need for new TB drugs

[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, and they should not be construed as reflecting any group consensus.

The next three workshops were held outside the United States, in South Africa on March 3–4, 2010 (IOM, 2011a); in Russia on May 26–27, 2010 (IOM, 2011b); and in India on April 18–19 and 21, 2011 (IOM, 2012). Each international meeting took the form of a collaboration between the IOM and national science academies in the respective host countries.[2] The fifth workshop was held July 31–August 1, 2012, in Washington, DC, and focused on the global supply chain for second-line anti-TB drugs (SLDs) (IOM, 2013). Box 1-1 presents the major messages that emerged from these previous gatherings, while Box 1-2 describes the nature of the threat of DR TB.

WORKSHOP CHAIR'S KEY MESSAGES

To underscore her remarks summarizing the themes of the workshop series, Gail Cassell, Visiting Professor, Harvard Medical School; and Vice President of TB Drug Discovery, Infectious Disease Research Institute, exhorted the workshop participants to consider how an accurate and comprehensive understanding of the realities of DR TB could be translated into policies to address the issues that are commensurate with the magnitude and urgency of the challenges. Cassell argued that several common public perceptions about DR TB have been shown in recent years, through the workshop series and other research and international meetings, not to accord with the reality of the disease. These perceptions include that TB is always treatable with available therapies, that the burden of DR TB is small compared with other unmet medical needs, and that DR TB rarely spreads from person to person. Cassell remarked that a failure to acknowledge the realities and to act rapidly to address the challenges would be catastrophic for many countries, adding that the effects would not be contained, as global public health would be jeopardized by way of international travel and immigration. Cassell concluded that a "polio approach" is needed—a focus on prevention, as was achieved with polio when the emphasis shifted from building more iron lungs to developing a vaccine.

THE BEIJING WORKSHOP

The sixth workshop was held in Beijing, China, on January 16–18, 2013, co-sponsored by the IOM and the Institute of Microbiology, Chinese Academy of Sciences (IMCAS). Box 1-3 describes the statement of task for the workshop.

[2] The South Africa workshop was co-hosted by the Academy of Science of South Africa; the Russia workshop was co-hosted by the Russian Academy of Medical Sciences; and the India workshop was co-hosted by the Indian National Science Academy and the Indian Council of Medical Research.

BOX 1-1
Themes of the Workshop Series

Gail Cassell, chair of the planning committee for the workshop series; Visiting Professor, Harvard Medical School; and Vice President of TB Drug Discovery, Infectious Disease Research Institute, laid out the common themes from the preceding workshops in her opening address at the meeting in Beijing:

- According to Cassell, the magnitude of the problem is "grossly underestimated." There were an estimated 310,000 (range of 220,000–400,000) MDR TB patients among notified TB patients in 2011 (WHO, 2012). But, she argued, considering that MDR TB is an aerosol-borne infection that is treated in just a small fraction of patients, this estimate is unreasonably low.
- Data from certain locations have demonstrated that most new cases of MDR TB result from person-to-person spread and are not caused by inadequate treatment, inappropriate drugs, or lack of patient compliance. In addition, Cassell noted, many have held a mistaken belief that MDR TB is caused by organisms that have a lack of fitness; this misperception has focused attention away from addressing transmission and has resulted in infection control receiving less attention than it should.
- Problems with the supply chain of SLDs have created major barriers to access, and these barriers will persist even if drug developers are successful at launching new therapies.
- Pediatric MDR TB remains a "silent epidemic" (Sentinel Project on Pediatric Drug-Resistant Tuberculosis, 2013). Children are often neglected by health care systems and the research communities (Seddon et al., 2013). Although exact numbers are unknown, it has been estimated that 100,000 children have MDR TB globally, but fewer than 500 children with MDR TB have been described in the medical literature to date (Ettehad et al., 2012).
- The number of patients receiving treatment is small, and their treatment often is ineffective. According to data from Salmaan Keshavjee, Director, Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, less than one-half of 1 percent of newly diagnosed patients have been treated since 2000. And even in the small proportion of patients who are being treated, many are not receiving high-quality drugs or drugs that specifically address their drug resistance profile, rendering treatment ineffective. As a result, millions of infected people are still in communities and likely to spread drug-resistant organisms.

continued

BOX 1-1 Continued

- Enhancing laboratory capacity may improve surveillance techniques and output but is unlikely to influence the treatment of individual patients, according to Cassell. In countries with fewer than one laboratory per 10 million population, including most high TB burden countries (HBCs), health care systems are not sufficient for scale-up at the speed needed to have a significant impact in making diagnosis and treatment more rapid, especially given that most patients are in remote settings.
- New and developing diagnostics increase speed and sensitivity but still require laboratory infrastructure. Technology for detection of MDR TB and extensively drug-resistant tuberculosis (XDR TB) at the point of care is available but, Cassell noted, requires further development and evaluation.
- When cases cannot be treated with available drugs, there is urgency to prevent transmission. Although the actual prevalence of TB that cannot be treated with any antibiotic therapies remains unknown, no consistent policies exist to deal with such patients. Proving that disease in these patients may be "untreatable" could take months, during which time they could spread the disease to others, noted Cassell.
- Successful treatment of potentially "untreatable" patients requires using three to four new classes of antibiotics simultaneously. Developing the needed medicines presents a huge technical and financial challenge. Developing a single new drug has been found to cost more than a billion dollars and to take more than a decade. Notwithstanding these resource needs, the total global investment for research and development (R&D) on TB drugs was just $649 million in 2011 (Treatment Action Group, 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.

As Cassell noted in the opening session of the workshop, the BRICS countries (Brazil, Russia, India, China, and South Africa) represent 43 percent of the world's population yet account for more than 80 percent of the world's cases of MDR TB. As the economies of these countries have grown, they have demonstrated remarkable success in ameliorating poverty and making progress against other communicable and noncommunicable

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 (FLD), originally developed and introduced in the 1950 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 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.

The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease ("The Union") 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,

continued

BOX 1-2 Continued

and much more expensive than those used to treat drug-susceptible TB. Despite the challenges, aggressive treatment with SLDs 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 DR TB (IOM, 2009).

BOX 1-3
Statement of Task for the Workshop

This public workshop in Beijing addressed the current status of DR TB globally, and in China. The workshop objectives were to

- consider lessons learned from the other three high burden countries;
- highlight global challenges to controlling the spread of drug-resistant strains;
- discuss innovative strategies to advance and harmonize local and international efforts to prevent and treat DR TB;
- consider urgent themes relating to the problem of MDR TB, XDR TB, and emergent TB strains that are potentially untreatable with drugs available; and
- consider the critical leadership role of the BRICS countries in addressing the threats and opportunities in DR TB.

diseases. These countries also have demonstrated their ability to achieve ambitious goals, such as hosting the World Cup and the Olympics.

China's political leadership has demonstrated a commitment to addressing DR TB, said Cassell. The 2012 publication in the *New England Journal of Medicine* of epidemiological results from China examining the country's burden of MDR TB represented a milestone in addressing the problem (Zhao et al., 2012). Shortly thereafter, the Minister of Health in China made treatment of MDR TB 70 percent reimbursable, making it only one

of five diseases in China for which this is the case. The Minister also has worked with manufacturers of SLDs to ensure that supplies are available and of high quality.

The magnitude and urgency of the problem demand that the best and brightest young investigators be fully engaged and passionate about achieving success, said Cassell. She cited the return of Lixin Zhang from the United States to China to serve as Deputy Director, Chinese Academy of Sciences Key Laboratory of Pathogenic Microbiology and Immunology; and Inaugural Director, Drug Discovery Center for Tuberculosis, IMCAS, as evidence of the engagement of investigators in China.

Cassell also called attention to an important meeting of the health ministers from the BRICS countries that occurred the week before the workshop (Box 1-4). The communiqué that emerged from that meeting represents a recognition by the BRICS countries of the need to take strong action.

ORGANIZATION OF THE REPORT

This report summarizes the presentations and discussions that occurred during the 3-day workshop in Beijing.

Chapter 2 draws on the initial and final sessions of the Beijing meeting to outline the challenges facing the BRICS countries and their unique capabilities to lead the fight against DR TB.

Chapter 3 summarizes the opening keynote address, delivered by Paul E. Farmer, Co-Founder, Partners In Health; Chair, Department of Global Health and Social Medicine, Harvard Medical School; and Chief, Division of Global Health Equity, Brigham and Women's Hospital, who examined the history of TB and pointed to a strategy—community-based care—that has changed the course of the epidemic in the past and could do so in the future.

Chapter 4 looks specifically at China. It describes the burden of DR TB in China, the health care delivery system in the country, and several factors that affect DR TB cases, including HIV infection and diabetes.

Chapter 5 examines programs addressing MDR and XDR TB in Russia, South Africa, Cambodia, and Ethiopia, which provide points of both contrast and similarity with programs in China and in the other BRICS countries.

Chapter 6 turns to DR TB in children, reviewing the global burden and transmission of pediatric DR TB and the challenges of diagnosis and treatment.

Chapter 7 explores issues of transmission and infection control, with a focus on the epidemiological, phenotypic, and genotypic evidence for primary transmission of DR TB. The chapter examines the role of infection

BOX 1-4
The Delhi Ministerial Communiqué

On January 10–11, 2013—the week before the IOM and IMCAS workshop in Beijing—the ministers of health from the five BRICS countries met in Delhi, India, at the Second BRICS Health Ministers Meeting. The communiqué issued at that meeting called for "the implementation of affordable, equitable and sustainable solutions for common health challenges." In particular, the 7th of 21 items in the communiqué stated:

> The Ministers recognized that multi-drug resistant tuberculosis is a major public health problem for the BRICS countries due to its high prevalence and incidence mostly on the marginalized and vulnerable sections of society. They resolved to collaborate and cooperate for development of capacity and infrastructure to reduce the prevalence and incidence of tuberculosis through innovation for new drugs/vaccines, diagnostics and promotion of consortia of tuberculosis researchers to collaborate on clinical trials of drugs and vaccines, strengthening access to affordable medicines and delivery of quality care. The Ministers also recognized the need to cooperate for adopting and improving systems for notification of tuberculosis patients, availability of anti-tuberculosis drugs at facilities by improving supplier performance, procurement systems and logistics and management of HIV-associated tuberculosis in the primary health care system.[a]

Other aspects of the communiqué related to DR TB include calls to face the continuing challenge of HIV, share existing resources, conduct effective health surveillance, enhance technology transfer, and provide universal health insurance. The Ministers also agreed to establish platforms for collaboration within the BRICS framework and with other countries with a view to realizing the goals and objectives outlined in the communiqué.

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[a] The text of the communiqué is available at http://www.brics.utoronto.ca/docs/130111-health.html (accessed October 4, 2013).

control in China and considers infection control policies and practices in other countries with a high prevalence of DR TB.

Chapter 8 looks at the current status and limitations of rapid diagnostic technologies. It describes the current use of diagnostic tests for drug-susceptible and DR TB in China and other countries, provides a laboratory and hospital-based perspective on drug susceptibility testing (DST), and reviews work on implementing programs for rapid diagnosis of DR TB.

Chapter 9 addresses diagnosis and treatment across the spectrum of drug resistance. It describes the prevalence of MDR, XDR, and potentially untreatable TB in key countries and considers the diagnosis and treatment challenges associated with defining and treating each.

Chapter 10 investigates ways of developing and strengthening the drug supply chain for DR TB. It considers to what extent and in what ways current supply chain mechanisms are or are not effectively accomplishing what is needed, in China and beyond. It also considers the current allocation of responsibilities and roles of the private and public sectors and examines opportunities for enhancing and optimizing collaboration.

Chapter 11 reviews the state of the art in TB research and identifies opportunities to apply new research tools to the problem of DR TB.

Chapter 12 summarizes a talk by Salmaan Keshavjee, Director, Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, that examined what, in his view, will be required to achieve zero deaths from DR TB.

Finally, Chapter 13 records discussions and presentations from the penultimate session of the workshop, which considered steps that could be taken to create an evidence-based blueprint for action.

2

The Challenges and Opportunities for the BRICS Countries to Lead

Key Messages[a]

- The BRICS countries are home to the majority of the global MDR TB patient population but are also engines of economic growth, funding a substantial portion of TB control worldwide.
- The BRICS countries could serve as sources of innovative ideas to develop and advance key areas of TB and MDR TB control.
- Poverty alleviation programs and free access to health care have helped Brazil keep MDR TB levels relatively low and focus on delivery system innovations such as community-based TB and MDR TB care.
- South Africa has made considerable progress in surveillance, infection control, better diagnosis methods, and the rollout of community-based MDR TB treatment, but challenges remain for effectively coordinating the currently siloed HIV and TB programs.
- India's national TB control program has the goal of seeking to ensure universal access to quality TB care for its 1.3 billion people in 600 districts. The complexities of TB care coordination across India's public and private sectors, poverty alleviation, active case finding, and treatment of latent TB are key challenges for the future.
- Russia has improved TB diagnostic capabilities, the availability of FLDs and SLDs, and infection control programs in recent years. Future steps to further improve the control of DR TB in Russia could include a shift in the TB care paradigm to more outpatient and community-

continued

Key Messages Continued

based services, as well as closer integration with the country's HIV program.

- Major health care system reforms undertaken in China include reducing the cost of MDR TB treatment for patients and improving the national TB surveillance system to provide individual patients with care as early as possible while generating data to facilitate the management of the disease from a population-based perspective. Opportunities for the future include applying China's strong scientific research capability to better understand the burden of disease and contribute to the development of new drugs to treat MDR TB.

[a] Identified by individual speakers.

As part of the final session of the workshop, several speakers provided reflections from the perspective of the BRICS countries. They were asked to discuss the leading role of the BRICS countries in the effort to combine science- and evidence-based policies with economic interventions to combat DR TB. After presenting an overview of the role of the BRICS countries overall in combating DR TB, this chapter summarizes remarks made by individual speakers concerning specific BRICS countries.

OVERALL ROLE OF THE BRICS COUNTRIES

Rifat Atun, Professor of International Health Management, and Head, Health Management Group, Imperial College London, noted that although the BRICS countries have been engines of economic growth, they also have been engines for the spread of MDR TB. Approximately 60 percent of the estimated 310,000 MDR TB cases among notified TB patients with pulmonary TB in 2011 were in China, India, and the Russian Federation, he observed (WHO, 2012).

The BRICS countries also provide a substantial portion of funding for TB control worldwide (Figure 2-1). Among 104 countries that account for almost 95 percent of TB cases globally, the BRICS countries have contributed an average of more than 60 percent of TB control funding since 2006. These countries also serve as a source for much of the funding for MDR TB. "Without the BRICS, global TB and MDR TB control efforts would collapse," said Atun.

Atun identified four areas in which the BRICS countries can play an

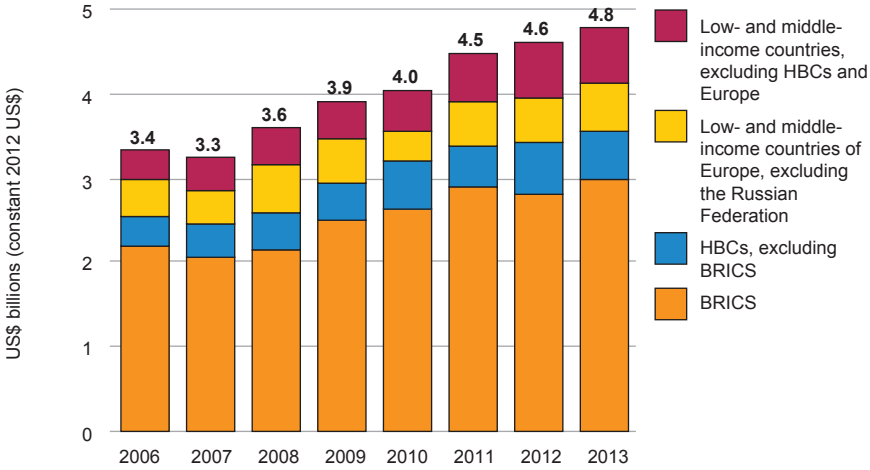

FIGURE 2-1 The BRICS countries provide the majority of funding for TB control in the 104 countries that account for 94 percent of global cases.
NOTE: BRICS, Brazil, Russia, India, China, and South Africa; HBC, high tuberculosis burden country.
SOURCE: WHO, 2012, Figure 5.1, p. 53. Reproduced with the permission of the publisher.

important role in combating TB and MDR TB. The first, he said, is filling the current gap in global leadership. Formation of the G20, for example, provides a new platform that could give a global campaign on TB control the visibility it urgently needs.

The sustained economic growth of the BRICS countries also provides an opportunity for new investment in TB control. For example, the percentage growth in gross domestic product of China's economy remains several times that of the European Union or the United States. If the BRICS countries invested in TB control at the same rate at which their economies are growing, the results would be large investments in local as well as global TB control.

Third, the BRICS countries have the opportunity to build on their current experience and become a major source of innovation in six areas related to TB control: (1) molecular biology and genomics; (2) epidemiology; (3) diagnostic tools; (4) new treatments and regimens; (5) new delivery models, including community-based models; and (6) assessment and evaluation, including of the optimal delivery model.

Finally, noted Atun, the BRICS countries are well positioned to lead global technical cooperation in TB control. These countries could foster

south–south cooperation, and they could also facilitate south–north cooperation, in which the global north learns from the global south.

The BRICS countries are emerging as an important voice in global economic, political, and financial discourse. They are achieving rapid economic growth, they are agents of innovation, they have almost half the world's population, in many sectors they are playing an important leadership role on the international stage, they have shown leadership in responding to HIV, they have been able to scale up TB control rapidly and successfully, and they have undertaken initiatives to achieve universal health care systems. "The BRICS countries can rise to the challenge of MDR TB treatment and control," Atun said. "Not just that, but I think they have the capability to transform global health."

BRAZIL[1]

Compared with the other BRICS countries, MDR TB levels have remained low in Brazil among both newly diagnosed and rediagnosed cases, for two major reasons. First, Brazil has had success in alleviating poverty through programs such as Bolsa Familia. Almost 40 million people were lifted out of poverty from 2003 to 2011 during the presidency of Luiz Inácio Lula da Silva. Second, in 1988, through enactment of the Federal Constitution, Brazil introduced free access to high-quality health care, and the Unified Health Care System has enabled a comprehensive response to the country's health challenges. Relatedly, Brazil has emphasized innovation not only in the development of drugs and technologies for high-burden conditions but also in the delivery of health care services and the manufacturing of health care products.

Brazil's family health program, which emphasizes primary health care that is delivered in the community, has been an important innovation. This community-based delivery system has been "the essence of the rapid achievements" in Brazil, said Atun. It is a proactive system that provides comprehensive care while fostering active outreach to communities and households, including those in congregate settings and difficult-to-access slums. The family health program is underpinned by a good information system, strong supply chains, and strong management. Atun characterized the program as being part of a community and civil society movement that has created an enabling platform for the treatment of TB and other conditions.

[1] This section is based on the presentations by Rifat Atun, Professor of International Health Management, and Head, Health Management Group, Imperial College London; and Jarbas Barbosa da Silva, Jr., Vice Minister for Health Surveillance, Ministry of Health, Federative Republic of Brazil.

Participating in a telephone call from Brazil, the Vice Minister for Health Surveillance, Ministry of Health, Federative Republic of Brazil, Jarbas Barbosa da Silva, Jr., noted that access to no-cost drugs has been an important part of the country's national TB program. At the same time, the drugs are not available for purchase in private drugstores, an approach that has helped prevent the development of MDR TB by reducing the injudicious use of drugs. Brazil also has made TB treatment a priority in primary health care delivery settings as a means of reaching the entire population.

The Delhi communiqué presents a concrete action plan in which each country serves as a nexus for different responsibilities, coordinating work in various areas—for example, Brazil in drug manufacturing, China in drug discovery and development, and Russia in medical technologies. At the next meeting of the ministers, in January 2014, the countries' experiences will be shared and adjustments made. The communiqué is a very important statement, said Barbosa da Silva, Jr., because it is comprehensive and applies both on a national and international scale. Thus, he said, it can play a critical role not only for the BRICS countries but for all countries that need to improve their health systems and the health of their populations.

SOUTH AFRICA[2]

The incidence of TB in South Africa is worse than that in many other countries, including the other BRICS countries, observed Kristina Wallengren, Clinical Advisor, KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH), Nelson R. Mandela School of Medicine, University of KwaZulu-Natal; and Chief Executive Officer, Tuberculosis and HIV Investigative Network of KwaZulu-Natal (THINK). The official figure is about 900 per 100,000 population, compared with about 110 per 100,000 in India, 75 per 100,000 in China, and just 4 per 100,000 in the United States. In KwaZulu-Natal province, the incidence of TB is more than 1,200 per 100,000 population.

The official incidence of MDR TB (2.3 percent in KwaZulu-Natal) is lower in South Africa than in many other countries, such as Russia, where it is above 20 percent. But because of the very high incidence of TB in South Africa, the absolute number of MDR TB cases is still high. KwaZulu-Natal province has an estimated 3,000 MDR TB cases each year, which is equal to 30 MDR TB cases per 100,000 population. Among MDR TB cases, about

[2] This section is based on the presentation by Kristina Wallengren, Clinical Advisor, KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH), Nelson R. Mandela School of Medicine, University of KwaZulu-Natal; and Chief Executive Officer, Tuberculosis and HIV Investigative Network of KwaZulu-Natal (THINK).

10 percent are XDR TB, and of the XDR TB cases, 88 percent are resistant to all 6 of the FLDs and SLDs that are tested routinely in KwaZulu-Natal.

Furthermore, the actual prevalence of MDR and XDR TB is likely to be substantially higher than currently measured. The observed level of MDR TB among the districts of KwaZulu-Natal province is proportional to the number of culture requests, which suggests that the actual rate of MDR TB in the province exceeds 100 per 100,000 (Wallengren et al., 2011). In addition, a postmortem study in a peri-urban public hospital in the province found that more than two-thirds of 240 deceased patients had TB, including 17 percent of patients in whom TB was not suspected (Cohen et al., 2010). The majority of the patients who were culture positive when they died, despite receiving TB treatment, were infected with drug-susceptible TB, suggesting that the diagnosis of TB was made too late to alter the course of their infection.

Wallengren described several areas in which some progress has been achieved, noting challenges that remain:

- *Surveillance*. Despite important progress, surveillance remains a major challenge in South Africa. The outbreak of XDR TB in Tugela Ferry detected in 2005, which demonstrated that XDR strains could readily be transmitted from person to person, was discovered "nearly by coincidence," said Wallengren. In light of a number of TB patients failing to thrive despite being on antiretroviral treatment (ART), two medical students in need of a project were assigned the task of collecting samples from all the TB patients at the Church of Scotland Hospital in Tugela Ferry and sending them to the provincial laboratory to be cultured. That laboratory had an unusual policy in place that called for testing all six FLDs and SLDs, not just the drugs requested by a physician. And the laboratory manager, to prepare for a conference, noticed in looking at some recent laboratory results that a large number of people from the hospital in Tugela Ferry were resistant to all six drugs. South Africa now has a centralized TB data system that enables surveillance, although there are still "some kinks" in the system, according to Wallengren. Nevertheless, the current system has greatly improved surveillance in the country.
- *Diagnosis*. Diagnosis is a particular challenge in South Africa because of the high HIV burden in the country. In KwaZulu-Natal province, 39 percent of pregnant women are HIV positive, and 70 percent of all TB cases are HIV positive. About 40 percent of TB cases in KwaZulu-Natal are smear negative, often also culture

negative, and are diagnosed instead through chest X-rays and clinical symptoms. Because TB is so prevalent, said Wallengren, HIV patients are put on TB treatment despite the absence of a confirmative bacterial diagnosis. The rollout of GeneXpert in South Africa has improved diagnosis of MDR TB. In the past, many patients with MDR TB died within a few weeks of having their sputum collected for testing. Diagnosis is faster with GeneXpert, which improves the outcomes of treatment and reduces transmission in the community. Better diagnosis also has revealed the extent of the problem in South Africa.

- *Treatment*. Treatment of MDR TB is improving in South Africa. The country has piloted and is starting to roll out community-based MDR TB treatment, and the initial results are promising. In addition, increased use of antiretroviral therapy has improved the prospects for patients with MDR TB. Problematically, however, the HIV and TB programs in South Africa remain siloed. Documentation and evaluation of the programs occur separately and do not reinforce each other. To the extent that the programs have been coordinated, the result has so far been simply a third silo: a combined HIV-TB program that interrelates poorly with the pre-existing programs.
- *Infection control*. Infection control also has improved dramatically in recent years, said Wallengren. At the time of the Tugela Ferry outbreak, few health care workers in the country knew what an N95 respirator was, but now they know that they should be wearing one routinely.

Finally, Wallengren described several important capacity-building initiatives in Africa. The Human Heredity and Health in Africa (H3 Africa) initiative is a consortium formed by the National Institutes of Health (NIH) and the Wellcome Trust to study genetic diversity in health and disease in Africa and develop the necessary expertise and networks among African investigators. K-RITH is an initiative undertaken by the Howard Hughes Medical Institute to conduct basic science research on TB and HIV and translate scientific findings into new tools for controlling these diseases. It is currently supporting investigations into a large variety of research questions, including the pharmacokinetics of TB treatment in children, new biomarkers and response to treatment, new diagnostic tools, assessment of drug resistance through whole genome sequencing, clinical trials of new treatment regimens, and investigation of the effects of anti-TB drugs on *Mycobacterium tuberculosis* (*M.tb.*).

INDIA[3]

India faces major challenges in diagnosing and treating MDR TB patients. It must reach 1.3 billion people in 600 districts, and each province has its own health care delivery system. The national TB control program has a small number of staff who must interact with a tremendously complex system. Nevertheless, said Salmaan Keshavjee, Harvard Medical School, "they have done a remarkable job."

About 1.5 million cases of TB are notified each year in India, including about 65,000 cases of MDR TB. Given global case-finding statistics, these estimates are likely lower than the actual numbers, said Keshavjee, which would put the actual number of MDR TB cases at roughly 100,000 per year. Furthermore, these numbers are only from the public sector, and the private sector treats an estimated 70 to 80 percent of all patients.

India's Revised National TB Control Program (RNTCP) has sought to ensure universal access to quality TB care throughout India. The RNTCP also has reached out to the private sector to promote the appropriate treatment of drug-susceptible TB. For example, it has become involved in medical college training, human resource development, and infection control to reduce the burden of both TB and MDR TB. The program has a goal of creating a nationwide network of more than 200 treatment sites that can enroll patients.

In the area of diagnosis, India has mounted a major effort since 2007 to modernize its testing of TB patients. It has established a network of culture and DST laboratories around the country, many of which are capable of line probe assays (LPAs). The goal for 2013 is to have 43 accredited public-sector laboratories and 22 private laboratories that are capable of undertaking drug-susceptibility testing for FLDs and SLDs and of diagnosing MDR and XDR TB. In addition, every province is to have at least one intermediate reference laboratory that can perform culture and DST and that has the associated infrastructure for getting samples to the laboratories and returning results to health care providers and patients.

Keshavjee listed several prominent challenges faced by India and other countries. Getting TB under control requires active case finding, not just waiting for very sick people to appear at TB facilities. Health care systems must look for contacts of patients and make sure that those contacts are treated. In addition, Keshavjee argued, given that patients with latent TB form a large part of the disease's reservoir, treatment of the latent phase of TB must be addressed in order to see large reductions in the incidence of disease.

[3] This section is based on the presentation by Salmaan Keshavjee, Director, Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School.

Keshavjee also argued that, because a large number of patients are treated outside of the public sector, private-sector health care in India needs to be mobilized and optimized. Doing so will require public–private partnerships that can, for example, modernize private-sector laboratories and reach patients who are using the private-sector system. Keshavjee cited as an example a recent project in Pakistan in which health workers screening private-sector patients increased case finding for TB by 400 percent, and this number was even higher for pediatric TB.

Finally, Keshavjee emphasized that improving the treatment of TB requires engaging with efforts to alleviate poverty. For example, Brazil's recent success in reducing the incidence of TB is due at least in part to its economic performance and to targeted programs that pay poor families to keep their children in school. When poverty was reduced, TB rates fell. Keshavjee noted that India is about to embark on a poverty alleviation program that will affect hundreds of millions of people, and evaluations of the effects of this program on TB rates will be of interest.

RUSSIA[4]

In recent years, Russia has improved both the diagnostic capabilities of its health care system and the availability of FLDs and SLDs, said Grigory V. Volchenkov, Chief Doctor, Vladimir Oblast TB Dispensary, Center of Excellence for TB Infection Control. Russia's efforts to address the transmission of DR TB have focused on health care settings, penitentiary settings, and other congregate settings. According to Volchenkov, a major program of infection control (discussed in Chapter 7) has brought the rate of occupational TB transmission in the Vladimir region to zero over the past 4 years. "We learned that we can make health care settings safer and less expensive," said Volchenkov. These savings have in turn freed up resources for diagnostics and treatments.

Volchenkov listed what he considered the most important steps for Russia to take to control DR TB:

- introduction of rapid molecular diagnostics for TB case finding at the subregional level;
- improved quality assurance in TB laboratories;
- sustainable supplies of FLDs and SLDs;
- strict adherence to evidence-based treatment regimens and directly observed therapy;

[4] This section is based on the presentation by Grigory V. Volchenkov, Chief Doctor, Vladimir Oblast TB Dispensary, Center of Excellence for TB Infection Control.

- a shift in the TB care paradigm from over-hospitalization to more outpatient services;
- closer integration with the HIV program; and
- the development and implementation of public health–oriented transborder TB control policies.

CHINA[5]

China has a great opportunity to provide leadership in addressing TB not only in China but around the world, said Yanlin Zhao, Vice Director, National Center for Disease Control and Prevention; and Director, National Tuberculosis Reference Laboratory, Chinese Center for Disease Control and Prevention (China CDC). But it also faces significant challenges posed by its high burden of MDR TB. Obtaining a fully accurate picture of the MDR TB burden in China remains difficult, particularly in vulnerable groups such as rural and migrant populations. Transmission control also remains a challenge, especially in facilities in remote areas that serve large numbers of patients. Yanlin Zhao said China is eager to learn from colleagues in other countries that have experience with community-based care and decentralized case management. In some provinces in which large numbers of men migrate to find work, rates of infection are high. Women may have lower rates of infection, but because of the persistent stigma associated with TB, they do not always get adequate care. And if care is not adequate, transmission of the disease is greater, which can lead to a higher prevalence of MDR TB.

To address these challenges, China recently enacted several major health care system reforms. MDR TB is now covered by medical insurance for all patients, with up to 70 percent of the cost of treatment being reimbursable, and this has significantly reduced the financial burden on MDR TB patients and their families. The health care system in China also has created a prevention network extending from the local to the national level to identify MDR TB patients and refer them to facilities where they can receive the proper treatment. This network is linked to a national TB surveillance system that provides patients with care as early as possible and also produces data for use in understanding the burden of MDR TB. These data, in turn, help with the management of diagnosis, treatment, infection control, health care worker training, and TB drug supplies.

[5] This section is based on the presentation by Yanlin Zhao, Vice Director, National Center for Disease Control and Prevention; and Director, National Tuberculosis Reference Laboratory, Chinese Center for Disease Control and Prevention (China CDC). Zhao was the first author of the "milestone" epidemiological study published in the *New England Journal of Medicine* in 2012, noted by Cassell earlier in the discussion (Zhao et al., 2012).

China has been acting both within the country and around the world to stop the spread of MDR TB and treat patients, Yanlin Zhao said. Although wealth alone cannot solve all problems, China's innovative and dynamic economic expansion can bring both new and existing solutions to bear in addressing the problem. Improved surveillance is creating a better understanding of the problem and of potential solutions, new diagnostic capabilities are being implemented across the country, and MDR TB treatment is becoming more accessible and affordable.

The Chinese government has been investing in diagnostic technologies, such as a biochip designed to enable identification and treatment of patients as rapidly as possible. The country has a strong scientific research capability to contribute to the development of new drugs and drug regimens and to bring that knowledge to the pharmaceutical industry so that quality products can be produced for patients in China and other countries. Chinese scientists and specialists continue to conduct investigative studies to understand the burden of TB, the disease strains, the effectiveness of infection control measures, and means of assisting vulnerable populations and to explore novel drug therapies.

China combines a fast-paced and fast-growing manufacturing sector with high-technology modern information management systems that can report data on diagnosis, treatment delivery, and treatment adherence from the local to the national scale, Yanlin Zhao said. For example, cell phones have been used in a pilot study to alert or remind patients to take medicine and also to convey information about side effects of treatment to physicians.

China has a long and, some might say, "patient" view of history, Yanlin Zhao concluded. But China today is a fast-paced country undergoing rapid change. Addressing the enormous challenge of MDR TB requires both patience and resilience because the problems are complex and multifaceted and cannot be solved overnight. But it also requires acting with a sense of urgency to provide treatment to all those with MDR TB in China, and to reduce the burden of MDR TB in China and the rest of the world. China has the capability to act quickly, said Yanlin Zhao. "China will, together with you, harness our individual and collective resources to break down the walls that impede treatment and [address] this challenge that we all face together."

3

Catching Up with the Microbe[1]

Key Messages[a]

- Divestment from TB control has been associated with outbreaks caused by DR TB.
- Community-based care has proven to be an effective way of combating TB, including that caused by drug-resistant strains, and can improve infection control.
- Novel diagnostics and therapeutics can be introduced equitably through "care delivery platforms" linking hospitals and clinics to patients in their homes.
- Sustained and substantial investments, and also new tools, are key in the strategy for catching up with microbial drug resistance and strengthening TB control.
- Many of these lessons are applicable to other chronic diseases, including those of noninfectious etiology.

[a] Identified by Paul E. Farmer, Co-Founder, Partners In Health; Chair, Department of Global Health and Social Medicine, Harvard Medical School; and Chief, Division of Global Health Equity, Brigham and Women's Hospital.

[1] This chapter is based on the presentation by Paul E. Farmer, Co-Founder, Partners In Health; Chair, Department of Global Health and Social Medicine, Harvard Medical School; and Chief, Division of Global Health Equity, Brigham and Women's Hospital.

As soon as antibiotic treatment for TB was introduced, resistance evolved; as each new antibiotic was introduced, resistance to that drug also emerged, observed Paul E. Farmer, Partners In Health, Harvard Medical School, and Brigham and Women's Hospital. The story is not much different for most pathogenic bacteria, parasites, and viruses: The "crisis of antibiotic resistance" is not new, and preventing or slowing its emergence calls for better infection control and for new delivery platforms that permit treatment of patients with multidrug regimens in a manner that is convenient to them. Given the long duration of therapy, the best approaches are usually community based, Farmer argued. All this is called for as the tubercle bacillus, like other pathogens, continues to adapt. The challenge to medicine, said Farmer, is to catch up with the microbe. "Are we going to win this struggle, or is the mycobacterium?"

MDR TB IN NEW YORK CITY

In the past, increasing wealth has had the effect of helping to reduce the burden of TB. For example, TB rates fell dramatically, albeit unevenly, in the United States and in other countries even before therapeutics became widely available. But the disease remained a ranking killer of young adults, especially those living in poverty, well into the 20th century. The decline in TB rates, hastened further by the introduction of effective therapies, led to a divestment from the TB control system. From 1944 through 1976, the U.S. Public Health Service continued to invest in TB control, but "block grants" to fund many TB services ceased in the 1970s (Figure 3-1). At that point, it was difficult to obtain funding for clinics or staff; research focused on the disease, including basic science and clinical trials, also faltered.

In the late 1980s, the incidence of TB in the United States began to rise in several major cities. The AIDS epidemic was believed to have a central role in this rise, although public health experts still debate exactly what caused the resurgence. Other contributing factors included a rise in homelessness, persistent urban poverty, immigration from TB-endemic regions, a weakened public health infrastructure, and limited access to medical care for the poor and marginalized—conditions that exist in many other cities around the world. A series of policies termed "the war on drugs" also led to a sharp rise in the prison population. The incidence of TB increased 132 percent in New York City from 1980 to 1990, with 14 percent of all U.S. TB cases occurring in New York by 1990.

The social determinants of TB epidemics also contribute to conditions that interrupt care; weaken the laboratory infrastructure needed for prompt diagnosis and for surveillance; lessen patients' ability to complete therapy once correctly diagnosed; and worsen infection control practices in clinics, hospitals, homeless shelters, and prisons. This, of course, is a recipe for

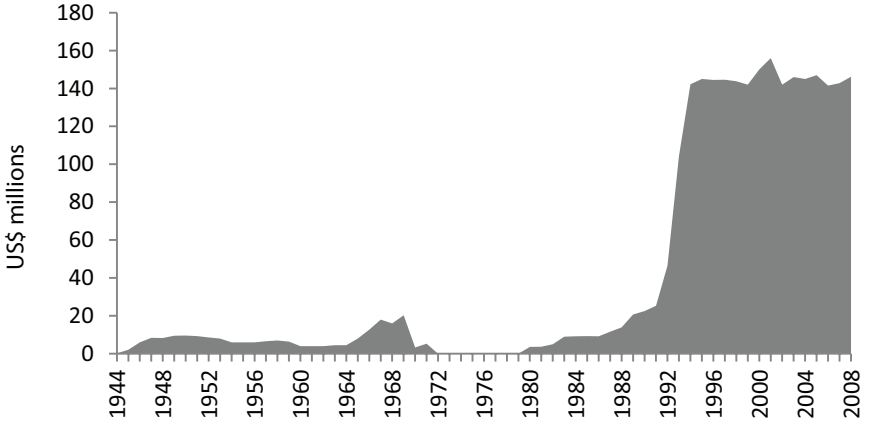

FIGURE 3-1 Funding for TB through block grants from the U.S. Public Health Service dropped to zero in 1972 but rose substantially after the epidemic of DR TB in New York City in the late 1980s and early 1990s.
SOURCE: Farmer, 2013. Presentation at the IOM workshop on the Global Crisis of Drug-Resistant Tuberculosis and the Leadership of the BRICS Countries: Challenges and Opportunities.

DR TB: By 1990, almost one in five patients with TB in New York City had MDR TB, accounting for 61 percent of the MDR TB cases in the United States.

After peaking in 1992, the number of TB cases, both drug-susceptible and DR, dropped rapidly in New York City and today is lower than it was before the increase (Figure 3-2). Several critical interventions helped turn the tide, including diagnosis using mycobacterial culture; access to quality-assured SLDs; proper infection control; and delivery of care under direct observation, with management of adverse events (Frieden et al., 1995). Also critical to the response was building a system for the delivery of these interventions. Many of these patients faced other problems, including poverty and homelessness, and the public health system, like some other social services in New York, had been weakened by reduced funding. At its best, the delivery system that helped to rein in the epidemic, which took many lives and cost by some accounts up to a billion dollars, offered prompt and accurate diagnosis, effective care with a multidrug regimen proven to be active against the infecting strain, and social services that helped vulnerable patients with a variety of problems ranging from housing to transportation to and from clinic. Much of the follow-up care was delivered by outreach workers who went to the patients. Indeed, community-based care played

1. Rates are based on official Census data.

FIGURE 3-2 TB rates in New York City rose to a peak in 1992 and then fell rapidly as new interventions were implemented.
SOURCE: Data from the New York City Department of Health and Mental Hygiene. Reprinted with permission.

a role, Farmer noted, in turning the tide in New York, and has since continued to contribute to TB control. Farmer suggested that community-based care should play a greater role in settings in which long-term hospitalization is ill advised because of a lack of infection control or the inconvenience for patients of being hospitalized far from home.

COMMUNITY-BASED CARE

In the United States, especially in areas with high incidences of HIV and poverty, community-based health care providers have been deployed to help manage TB for three decades. Community-based care of TB, which Farmer referred to as an enabling platform, is "one of the best ways to promote infection control and to prevent transmission within institutions even as it boosts cure rates." This delivery system, while not a new drug or new diagnostic, is an important innovation nonetheless: It can be effective not just for TB, he argued, but also for other chronic infectious diseases, including AIDS and hepatitis C, and for diabetes, epilepsy, and other chronic afflictions requiring daily therapy.

Community-based care relying on community health workers has not evolved much in the United States, but recent developments designed to improve health outcomes, increase coverage, and decrease costs should make such models much more common in the treatment of chronic disease, regardless of etiology. Nor has community-based care taken hold in the BRICS countries, with a few notable exceptions entailing DR TB programs. In China, once famous for its "barefoot doctors," community-based care is no longer as prevalent as clinic-based or hospital care, Farmer noted. Existing community-based systems have been weakened in rural areas and new ones have not yet been built as the economy has boomed, and China has become increasingly urban. Hospitals and specialty clinics are of course necessary, "but community-based care is crucial to good outcomes for chronic diseases [that are] prevalent," said Farmer. Addressing the problem of community-based infrastructure will be central to dealing effectively and humanely with DR TB in China. Increasing wealth will help with TB control in China, as it has elsewhere, but "economic growth alone will not solve all problems," Farmer said, "nor will it suffice to address drug-resistant TB here or in India, South Africa, or Russia."

Early diagnosis, proper treatment, and better infection control can be applied anywhere in the world. Farmer gave two examples from his experience. Like other cities in South America and much of the rest of the world, Lima, Peru, has peri-urban slums. Patients with DR TB in the poorest reaches of Lima were said to be "untreatable," but carefully designed multidrug regimens proved effective in more than 80 percent of MDR TB patients who had failed numerous retreatment regimens. This program

was later brought to scale through the national TB program, a stunning achievement. Even among Peruvian patients retrospectively identified as having XDR TB, again often termed "untreatable," roughly 60 percent were cured through a comprehensive treatment program that included aggressive management of adverse events, nutritional and social support (including regular group therapy sessions), opportunities for participation in microfinance initiatives and job training, follow-up screening for recurrent disease, and efforts to reduce household and institutional transmission (Mitnick et al., 2003).

Community-based care was central to this success. The treatment regimen was grueling, including intramuscular injections, often for a year. But the patients almost never refused treatment once it was made clear that the regimens were designed based on DST; with proper social support from their community health worker (and from nurses and other providers), they rarely dropped out of care. Whether delivery platforms are convenient or inconvenient will affect compliance. But the idea that patients often refuse effective treatment, even if difficult, is "a fiction," said Farmer. "The great majority of patients want to be treated, but they do not want another *ineffective* and prolonged regimen, which is what most of them received prior to initiating care for laboratory-proven MDR TB." The intensive treatment regimen for MDR TB was scaled up to thousands of patients in Peru, which was then reporting the largest number of new TB cases in Latin America, most of them caused by drug-susceptible strains. The Peruvian experience suggests that, with the needed resources and right partnerships, national TB programs can successfully integrate care for those types of TB that are more difficult to diagnose and cure, suggested Farmer.

Another example Farmer cited was that of Rwanda, which in 1994, after the genocide, was by many criteria the poorest country in the world. Almost 20 years later, it is the only country in sub-Saharan Africa on track to meet all the health-related millennium development goals. Declines in child mortality in Rwanda during the past decade have been the steepest in the world, and mortality due to AIDS, TB, and malaria has also plummeted, as have deaths in childbirth. Many of the people who have been lifted out of poverty in recent years are in the BRICS countries, but Rwanda is also an impressive model of progress (Farmer et al., 2013).

The community health model has made a major difference in the AIDS program in Rwanda. Rwanda, along with much-richer Botswana, has the largest and most widespread access to HIV care in Africa; both are set to reach universal access to care. The quality of this care is greatly increased by including community health workers in the routine care of patients receiving antiretroviral therapy. Of more than 1,000 patients in a community-based AIDS treatment program in rural Rwanda, more than 90 percent were retained in care after 2 years (Rich et al., 2012). The outcomes of MDR

TB treatment in the first cohort of Rwandan patients were as good as those registered in Peru, even though there was much more HIV coinfection in Rwanda. Enabling platforms reliably link community-based care to health centers, to hospitals, and even to prisons, Farmer said. "That is one reason why, in countries as diverse as Peru and Russia and Rwanda and Lesotho and the United States, the outcomes of community-based therapy of drug-resistant TB, even among patients held to be 'untreatable,' are consistently good and quite similar. They will be further improved with prompt diagnosis and with better regimens and improved infection control, as long as these innovations are included in this enabling platform."

THE NEED FOR RESOURCES

Resources are a critical element of success. Much more funding has gone to stemming the AIDS epidemic in recent years than to fighting TB. Money is not everything, Farmer admitted, and TB is a leading comorbidity of AIDS, but resources clearly make a difference, especially when they help resolve false debates commonly seen regarding epidemics that afflict primarily poor people. He noted by way of example that prior to the advent of resources it was common to argue that, for those living in poverty and with AIDS, prevention and care were necessarily pitted against each other. He also cited arguments about the need to determine which interventions were cost-effective and which were not. These same debates have recurred not only for DR TB but also for other pathologies, including most cancers, held to be "untreatable" in settings of poverty long bereft of robust health infrastructure and skilled personnel and the resources to build and train and support them. False "competitions" have hobbled TB control for many decades, Farmer said—prevention *versus* treatment, research *versus* delivery, domestic *versus* international, HIV positive *versus* HIV negative, drug-susceptible *versus* drug-resistant. "This either-or approach has been a very limiting way of thinking about a complex illness that is chronic and requires massive investment."

Poverty reduction has helped reduce premature mortality in parts of Africa, and it is having an even more striking effect in China. According to the World Bank, China's poverty rate has fallen from 85 percent to 16 percent in recent decades. China thus accounts for much of the world's reduction in poverty. But economic growth does not solve every health care problem, Farmer repeated in closing. Great social and economic disparities and rapid social and economic change can contribute to an increase in DR TB (and other pathogens) even as overall disease burden falls. This is occurring in many countries now. A focus on equitable access to humane and effective care is an important step in reversing growing health disparities. Moving resources internally within a country—from where they are

typically concentrated to where they are most needed—poses significant challenges. Multidrug regimens administered for an appropriate duration will be essential until new methods of preventing and curing TB are developed. The acquisition of drug resistance in the microbes needs to be slowed through prudent but equitable access to new tools, from rapid diagnostics to novel agents effective against *M.tb.*, and through new approaches that move safe and effective care to the communities in which patients and their families live and work. At the moment, many TB programs are not sufficiently resourced to catch up with the microbe.

Partnerships will be essential to deal with these and other complex health problems. Cooperation should be south–south as well as south–north, Farmer said, but also with those most affected by the disease, the patients and their families. Collaborations among universities, the public sector, and community health workers have proven their effectiveness in diverse settings when a patient-focused approach is embraced. When the best diagnostics and therapeutics are available as part of an equitable and humane delivery platform, many lives can be saved and many new infections averted.

The BRICS countries have, or are mustering, the technological and financial resources to enable innovation. Building an equitable and humane delivery platform will require further resources. "A lot of the answers for this global challenge are likely to come from China and from some of other countries we are calling the BRICS countries," Farmer predicted. "I am confident that these problems, including drug-resistant TB and rising health disparities, must and will be addressed here, and that the rest of the world will learn."

TB can be addressed effectively, Farmer concluded, only by "significant and sustained investments in protecting public health, not just in one corner of the global economy, but everywhere."

4

Drug-Resistant TB in China

Key Messages[a]

- According to national surveillance results, China has the second largest MDR TB burden among 27 MDR TB HBCs.
- As China has accumulated experience with MDR TB control, new models, new diagnostic methods, and new funding mechanisms have been implemented.
- Many MDR and XDR TB patients are treated at hospitals in China, and studies have shown that transmission is occurring in these settings.
- China's capacity to conduct DST remains limited.
- HIV infection and other health problems such as diabetes contribute to the problem of MDR TB in China.

[a] Identified by individual speakers.

China has a population of more than 1.3 billion and a per capita gross domestic product of about $5,400. Several speakers at the workshop described the status of DR TB in China and efforts to control the disease. Participants discussed the results of a drug-resistance surveillance released in 2012, which provided crucial information that is being used to shape the country's programmatic management of MDR TB. As they sought to explore multiple aspects and characteristics of the epidemiology of MDR

TB in China, participants also discussed the country's MDR and XDR TB regimens, the treatment of MDR TB in hospitals, the role of HIV infection, and diabetes as a comorbidity in TB patients.

MANAGEMENT OF MDR TB IN CHINA[1]

Mingting Chen, Vice Director and Researcher, National Center for Tuberculosis Control and Prevention, China CDC, described survey information on China's MDR TB prevalence and treatment and prevention approaches.

Results from the 2010 Fifth Nationwide TB Prevalence Survey in China show that all types of TB declined to 459 per 100,000 in 2010, compared with 466 per 100,000 in 2000. Smear-positive TB declined from 169 per 100,000 in 2000 to 66 per 100,000 in 2010—a "remarkable decrease" of about 61 percent, said Mingting Chen. Bacteriologically confirmed TB fell from 216 per 100,000 in 2000 to 119 per 100,000 a decade later, a decrease of 45 percent. China has 100 percent coverage of Directly Observed Treatment-Short course (DOTS), its case detection rate of new TB cases is 80 percent, and its cure rate for new TB cases is above 90 percent. More than 4.5 million smear-positive patients were cured from 2001 to 2010, and China achieved its millennium development goal for TB control 5 years ahead of schedule.

Chen laid out the steps necessary to prevent MDR and XDR TB. First, the quality of basic DOTS needs to be enhanced by consolidating a strong government commitment, improving the TB laboratory services network, and improving identification and care of TB patients in vulnerable groups. In addition, the recording and reporting system for TB needs to be strengthened, the quality of FLDs and SLDs needs to be improved, standard operating procedures in drug supply and management systems need to be implemented, and cooperation between public health institutions (such as China CDC) and hospitals needs to be intensified.

China has undertaken technical support for the treatment of MDR and XDR TB patients, providing national guidelines for the management of DR TB, issued in 2012 by China CDC; a manual for management of SLDs; guidelines for infection control; guidelines for adverse reactions to DR TB chemotherapy; and standard operating procedures for culture and DST. China also has launched a pilot project for the programmatic treatment and management of MDR and XDR TB patients (PMDRT). This initiative includes the formulation of a national framework and working plan for the PMDRT, as well as a gradual increase in the number of pilot

[1] This section is based on the presentation by Mingting Chen, Vice Director and Researcher, National Center for Tuberculosis Control and Prevention, China CDC.

sites for implementation of drug resistance surveillance. The project also involves improving laboratory services at each level so they can meet the standards for MDR TB diagnostic tests, such as TB culture and DST. A projected future laboratory network for China would include various levels of laboratory services and diagnostic technologies at coverage levels ranging from the county to the entire nation (Table 4-1). Also, as part of treatment for MDR and XDR TB patients, the national drug resistance surveillance effort selected 70 counties as survey sites and enrolled more than 4,600 smear-positive patients, including 3,500 new patients and 1,100 retreatment patients. At the provincial level, 20 of China's 30 provinces conducted drug-resistance surveys, with support from WHO, the Global Fund, and local governments. In addition, the Ministry of Health conducted a survey to determine stakeholders' attitudes toward policies aimed at combating MDR and XDR TB to predict the cost-effectiveness of the PMDRT and to provide support for the PMDRT among policy makers.

China has established a model of cooperation between hospitals and public health centers, Mingting Chen said. Hospitals have responsibility for diagnosis, treatment, and side effects for MDR TB patients. China CDC has the responsibility for management, supervision, follow-up, detection, and drug management. Both have responsibility for reporting information to TB management information systems.

The PMDRT has received support from the Global Fund. In addition, the Bill & Melinda Gates Foundation (BMGF) has supported the development of new models, new tools, and new techniques for preventing and controlling MDR and XDR TB. This support has enabled evaluation of a number of new diagnostic technologies, including LED (light-emitting diode) microscopy, LAMP (loop-mediated isothermal amplification), the Hain test, Genechip from Boao Technical Company, and GeneXpert. In addition, China has accelerated the assessment and implementation of rapid diagnostic methods through internal initiatives and partnerships with international organizations.

These experiences have contributed to the development of an action plan for regulating the use of SLDs, building a new financing mechanism for MDR TB control, establishing MDR TB treatment and management sites at the prefecture level, fostering cooperation between TB dispensaries and other health services, enhancing human resources, and designing an appropriate case-finding strategy. High-risk populations have priority, said Chen, after which all smear-positive patients will receive screening tests for MDR TB.

The National Tuberculosis Plan, published in November 2011, calls for building up the laboratory network by 2015 so that more than 80 percent of county TB laboratories can conduct sputum culture tests, all prefecture-level laboratories can carry out DST, and all regional-level laboratories can

TABLE 4-1 Projected Future TB Laboratory Network in China

	LED Microscopy	Solid Culture and DST	Solid DST	Molecular Test	Liquid Culture and DST	Biosafety
Supranational Level/ National Level	Yes	Yes	Yes	Yes	Yes	P3 and P2
Provincial Level	Yes	Yes	Yes	Yes	Maybe	At Least P2
Prefecture Level	Yes	Yes	Yes	Yes	Maybe	P2
County level	Yes	Maybe	No	Maybe	Maybe	P2

NOTE: DST, drug susceptibility testing; LED, light-emitting diode.
SOURCE: Mingting Chen, 2013. Presentation at the IOM workshop on the Global Crisis of Drug-Resistant Tuberculosis and the Leadership of the BRICS Countries: Challenges and Opportunities.

perform strain identification (Table 4-1). In addition, MDR TB management will be expanded so that by 2015, prefecture-based MDR TB management will have reached 50 percent, and the screening rate of patients suspected of having MDR TB will have reached 60 percent. The scale-up plan of the PMDRT for 2012 to 2015 has been designed to enhance training for TB dispensary staff and supervision for MDR TB work. The plan also calls for organizing monitoring missions to supervise the plan's implementation, along with quarterly notification of target accomplishment status, the development of local TB control programs, and application for sustainable funding once Global Fund support ends.

Funding is critical for the future of TB and MDR TB control in China, Mingting Chen noted. Funding comes from a combination of sources, including governments, insurance, and patients. In July 2011, the Ministry of Health issued a policy on integrating MDR TB treatment into medical insurance for rural residents, with 70 percent reimbursement, 20 percent medical aid, and 10 percent self-payment. By July 2012, MDR TB had been integrated into the local National Rural Medical Care System pilots in 25 provinces, ensuring more than 70 percent compensation.

Mingting Chen added in conclusion that legislation is important to govern the isolation and travel of MDR TB patients. Also important is evaluation of China's efforts to control and prevent MDR TB.

2007 NATIONAL SURVEY OF DRUG RESISTANCE IN CHINA[2]

The drug resistance surveillance effort that released its results in 2012 had several goals, said Yanlin Zhao, China CDC:

- To interpret the epidemiological status of DR TB in China.
- To analyze the risk factors for drug resistance occurrence among TB patients.
- To explore the biological characteristics of the predominant mycobacterium bacillus in China.
- To understand the micro-evolution of the prevalent strains in China.

Seventy clusters, or sites, were selected according to new smear-positive cases reported by each province relative to the total number of cases nationwide in 2004 and 2005, with all provinces having at least one cluster. Susceptibility testing was conducted for six anti-TB drugs: ethambutol, isoniazid, kanamycin, ofloxacin, rifampicin, and streptomycin. Equipment, reagents, records, and questionnaires were standardized for all the sites, and the survey workers received centralized training. The work of all the clusters was supervised, with special support for priority sites.

The survey revealed an MDR TB rate of 5.7 percent among new cases and 25.6 percent among previously treated cases, with a combined rate of 8.3 percent (Zhao et al., 2012). XDR TB rates were 0.47 percent for new cases, 2.06 percent for previously treated cases, and 0.68 percent overall. Furthermore, among new cases, 1.8 percent of patients with MDR TB were already resistant to ofloxacin or kanamycin, as were 8.5 percent of previously treated patients. According to Mingting Chen, the survey results indicate that China has the second-largest MDR TB burden among 27 HBCs.

Among the patients who completed treatment, the majority did so at China CDC facilities (Figure 4-1). The patients who did not complete treatment were more likely to have received that treatment at general hospitals or private facilities. In addition, one of the risk factors for DR TB among previously treated patients was receiving two or more treatments at TB hospitals or other medical facilities. Closer cooperation is needed between the China CDC and other medical facilities to reduce these gaps, said Yanlin Zhao.

To prevent MDR TB, new tools are needed to detect suspected cases of MDR TB and to base treatment regimes on resistance tests. Patients starting treatment in hospitals need follow-up after discharge until they complete the regimen. A better linkage between the hospital system and

[2] This section is based on the presentation by Yanlin Zhao, Vice Director, National Center for Disease Control and Prevention; and Director, National Tuberculosis Reference Laboratory, China CDC.

FIGURE 4-1 The majority of MDR TB patients who completed treatment did so at China CDC facilities.
SOURCE: From the *New England Journal of Medicine*, Zhao, Y., S. Xu, L. Wang, D. P. Chin, S. Wang, G. Jiang, H. Xia, Y. Zhou, Q. Li, X. Ou, Y. Pang, Y. Song, B. Zhao, H. Zhang, G. He, J. Guo, and Y. Wang, National survey of drug-resistant tuberculosis in China, 366(23), 2161–2170. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

China CDC could improve the treatment provided by hospitals, strengthen infection control, and enhance follow-up after discharge. When MDR TB is detected in a patient, the patient is referred to a specialized hospital for second-line treatment. These specialized hospitals need to be strengthened and linked to the China CDC system, Yanlin Zhao said. China CDC maintains an ongoing DOTS program that uses smear microscopy for diagnosis, empirical treatment using a standardized regimen of FLDs, and community case management. Collaborations between China CDC and hospitals can improve the capability for rapid molecular diagnosis of TB and provision of diagnosis-based treatments. In addition, community-based care management can help ensure that a patient follows the treatment regimen. The use of mobile phones and medical monitors can support community case management.

Preventing DR TB among new cases requires identifying patients with no prior diagnosis of TB who were given TB drugs. They likely were suspected to have TB and started on TB drugs but did not receive a proper diagnosis. If they took TB drugs improperly for a sufficient period of time, MDR TB may have developed.

It is important to "turn off the tap" of DR TB, said Yanlin Zhao. Current factors causing drug resistance to develop will lead to the rapid loss of effectiveness of any new drug. Especially as new drugs become available, it is critical to improve systems, adopt new diagnostics, and use new drugs in a rational manner to prevent the development of drug resistance. In particular, the level of quinolone resistance has implications for the development and use of new regimens using that drug. The fact that one-third of MDR TB cases have quinolone resistance may limit the use of new regimens for MDR TB.

Yanlin Zhao is involved with an effort to collect and sequence strains of the bacterium, which makes it possible to do cluster analysis of cases. These data can be used to answer such questions as

- What is the population structure of the prevalent TB strains in China?
- What advantages do they have to become the prevalent strains?
- How do the prevalent strains interact with hosts and the environment?
- What are the risks to health care workers, and are infection control measures effective?

Finally, Yanlin Zhao briefly described plans for the next survey of drug resistance in China. The survey will continue to use the 70 clusters as sites, which will enable tracking prevalence over time. It will be possible to compare regions and genotypes to determine the effects of economic and

cultural forces and to use this information to inform individualized case management.

THE DIAGNOSIS AND TREATMENT OF MDR TB IN HOSPITALS[3]

When patients are diagnosed with TB in China, they receive the DOTS regimen of four drugs for 6 months, said Wenhong Zhang, Professor of Medicine, and Director, Division of Infectious Diseases, Shanghai Huashan Hospital, Fudan University. If patients have a previous history of treatment, they receive DOTS-Plus in addition to another medication for 8 months. If treatment fails, patients are transferred to a higher-level facility such as a TB hospital.

Because of these procedures, hospitals in China accumulate many DR TB cases. These cases differ from cases in other countries with a low disease burden, such as South Africa or the Americas, Wenhong Zhang emphasized. For example, the 2-month sputum conversion rate is much lower in China than in Western countries.

In a study of patients with MDR TB 4 years after standardized FLD treatment, it was found that the overall recurrence rates among new and retreatment cases were 46 percent and 66 percent, respectively; the overall death rates among new and retreatment cases were 25 percent and 46 percent, respectively; and 40 percent of the traced new cases and 24 percent of the retreatment cases were alive and without recurrent TB (He et al., 2010). These grim data highlight the importance of detecting MDR TB so that these patients are not given the standard DOTS regimen, which can augment the evolution of MDR and XDR TB, Wenhong Zhang said.

According to data from Hunan province (Deng et al., 2011), the rate of resistance to SLDs among MDR TB patients was almost 60 percent, including 53 percent to fluoroquinolones, 18 percent to amikacin, and 22 percent to capreomycin. The overall rate of XDR TB among these patients was a "very high" 18.7 percent. The high rate of fluoroquinolone resistance is especially troubling because the outcome of treatment often depends on this factor.

MDR and XDR TB can be either acquired from treatment or transmitted by other patients, but the relative importance of these two pathways in China is unknown. Citing a paper that had not yet been published at the time of the workshop, Wenhong Zhang said that he and his colleagues demonstrated the existence of XDR TB transmission in a provincial TB hospital through studies of more than 3,000 strains. They also were able to track the evolution of the strains toward greater drug resistance. These

[3] This section is based on the presentation by Wenhong Zhang, Professor of Medicine, and Director, Division of Infectious Diseases, Shanghai Huashan Hospital, Fudan University.

data point toward the role of person-to-person transmission and the importance of quarantining MDR and XDR TB patients to contain the spread of disease, Wenhong Zhang said.

Wenhong Zhang and his colleagues also have examined a number of risk factors for MDR TB, including the frequency of hospital visits, age, occupation, and history of TB treatment. Two risk factors are particularly prominent: a history of TB treatment and delay in the diagnosis of TB. The results of sputum smear tests after 2 months of treatment are very important for treatment decisions as well. Wenhong Zhang also commented on the new policy in China, effective in 2010, providing that the China CDC would no longer treat patients but would provide management, supervision, and follow-up. He noted that lack of awareness that a patient should be followed up by China CDC is another MDR TB risk factor.

WHO recommends that all patients with suspected TB be tested for drug susceptibility. In treatment failure and retreatment cases, it recommends rapid DST for isoniazid and rifampicin resistance and treatment of patients empirically with second-line regimens until the test results are available. The capacity for DST in China remains limited. Most TB patients are in county hospitals, not in TB hospitals. As a result, the majority of patients cannot be tested for drug susceptibility. In 2008, China had just 52 laboratories able to conduct DST. That number has since grown to 81 and will exceed 100 in the next 2 years. Citing an article in preparation at the time of the workshop, Wenhong Zhang said that he and his colleagues have demonstrated the value of a new-generation polymerase chain reaction (PCR)-based LPA in detecting resistance to ethambutol, kanamycin, and ofloxacin. This assay could function as a supplement to traditional DST, he said, allowing for better treatment decisions in China.

Many factors affect the health outcomes of patients, Wenhong Zhang concluded, including the absence of DST for all patients, the duration of treatment, the lack of effective vaccines and high-quality drugs, the emergence and transmission of drug-resistant strains, and weak health systems in resource-poor regions. He suggested that a massive funding and political commitment is needed in China to ensure that the aims of the WHO Global Plan to Stop Tuberculosis 2006–2015 are achieved.

MDR AND XDR TB CHEMOTHERAPY IN CHINA[4]

According to Shou-Yong Tan, President, Guangzhou Chest Hospital, a treatment regimen for MDR or XDR TB should include pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide),

[4] This section is based on the presentation by Shou-Yong Tan, President, Guangzhou Chest Hospital.

and cycloserine, or PAS (para-aminosalicylic acid) if cycloserine cannot be used. It also should include at least four SLDs likely to be as effective as pyrazinamide during the intensive phase of treatment.

Strategies for treatment can be standardized, empirical, or individualized. The standardized treatment, to be given when DST is unavailable, is based on data from drug resistance surveillance in a representative patient population. The empirical treatment is based on each patient's past history of anti-TB therapy. The individualized treatment is based on each patient's past history of anti-TB therapy and the current results of DST.

The Guangzhou Chest Hospital TB Department has been exclusively responsible for the diagnosis and treatment of MDR TB in the Guangzhou region. All patients have been treated with the Global Fund MDR TB treatment regimen. From July 2008 through December 2012, 800 TB cases were treated, with 183 having MDR TB and 19 having XDR TB. Of all MDR TB patients who completed 24 months of standardized treatment, 30 (54.6 percent) were hospitalized, including 14 (25.5 percent) with hospital stays longer than 1 month. Among these patients, the cure rate was 63.3 percent, which was significantly higher than that in nonhospitalized patients. The failure rate in hospitalized patients was 23.3 percent, which was comparable to that for nonhospitalized patients. The dropout rate among hospitalized patients was just 6.7 percent, which was significantly lower than the overall dropout rate of 18.2 percent.

Overall mortality was 12.7 percent. The mortality in hospitalized patients was 6.7 percent, again significantly lower than for nonhospitalized patients. The overall cure rate for XDR TB patients who completed the 24-month standardized treatment was 0 percent.

According to these results, the hospitalized patients had a higher cure rate, a lower dropout rate, and lower mortality than the nonhospitalized patients. However, this regimen failed in all XDR TB patients. Irregular treatment or an unsatisfactory regimen, including unreasonable drug combinations, inadequate dosing, or a duration of treatment less than 24 months, are major factors linked to treatment failure.

Some MDR and XDR TB patients at the hospital also have undergone individualized treatments involving the use of immunomodulators, surgery, or other interventions, said Shou-Yong Tan. The cure rate, failure rate, and mortality among patients receiving such treatments were comparable to those for patients receiving the standardized treatment. Immunomodulators, surgery, or other interventional procedures showed modest impacts on treatment outcomes.

DRUG-RESISTANT TB AND HIV IN CHINA[5]

The Guangxi Zhuang Autonomous Region is located in the southern part of China, north of Vietnam, said Liu Feiying, Guangxi Zhuang Autonomous Region Center for Disease Control and Prevention, China. It has a population of about 50 million, 38 percent of whom are minorities, living primarily in the 70 percent of the region covered with mountains and hills.

Guangxi has a high burden of TB and HIV infection, with the second highest rate of HIV infection in China. However, the prevalence of infection with *M.tb*. and nontuberculous mycobacteria (NTM) in HIV-infected patients in China is unknown.

Feiying described a recent study that estimated the prevalence of *M.tb*. and NTM in HIV-infected patients in Guangxi province, determined the drug resistance of *M.tb*., and evaluated the genotypic patterns of *M.tb*. strains. Samples were collected from two HIV-designated hospitals in Guangxi from 2005 to 2008 and cultured using liquid and solid methods. HIV-infected patients with positive mycobacterial cultures were included. Drug resistance testing was performed by the proportion method. NTM species were identified by sequencing 16S rRNA, and the *M.tb*. isolates were genotyped using the VNTR (variable-number tandem-repeat) method.

From 2005 to 2008, a total of 1,233 HIV-infected patients were screened for TB infection in Guangxi. Eighteen percent—or 219—had a specimen that was culture positive for Mycobacterium species. Among these culture-positive patients, 53 percent had *M.tb*., and 47 percent had NTM. The majority of the isolates reflected pulmonary TB. The median CD4 count for 154 of these patients was only 35. CD4 counts were lower for patients with NTM than for *M.tb*. patients. Twelve NTM species were identified from the 102 NTM isolates, with *M. avium* complex being the most frequent.

Among the 111 *M.tb*. isolates with drug susceptibility test results, 27 percent were resistant to at least 1 FLD. Of these, 67 percent were new TB cases. Twelve patients had MDR TB, which was diagnosed in 8 of 20 previously treated TB cases and in 4 of 91 new TB cases. All 12 of the MDR TB patients were younger than 45 years old.

Among the 117 *M.tb*. isolates, 105 different genotypic patterns were identified; 97 isolates had unique genotype patterns, and 20 isolates were identified as cluster strains belonging to 8 different clusters. Beijing family strains accounted for 67 percent of *M.tb*. isolates, and 74 percent of isolates from patients aged less than 40 years old were of the Beijing genotype.

[5] This section is based on the presentation by Liu Feiying, Guangxi Zhuang Autonomous Region Center for Disease Control and Prevention, China.

The high rate of MDR TB in previously treated HIV-infected patients in Guangxi indicates the need for effective management and treatment of patients with both TB and HIV, Feiying concluded.

MDR TB AND DIABETES[6]

Duan Hongfei, who presented a talk prepared by Chu Naihui, Beijing Chest Hospital, Capital Medical University, remarked that diabetes is a serious problem in China—there are more diabetes patients than TB patients. A 2008 national survey estimated that 90 million adults in China have diabetes, and more than 140 million adults have prediabetes (Yang et al., 2010).

In 2011, WHO and The Union launched a collaboration for the care and control of TB and diabetes (WHO and The Union, 2011). Also in 2011, dual screening of TB and diabetes was launched in some facilities in China. A study of screening of TB patients for diabetes in China was published in 2012 (Li et al., 2012). The study covered 6 facilities and 8,886 registered patients with TB. Among these TB patients, 1,090 with diabetes were identified, including 227 in whom diabetes was newly diagnosed. According to these numbers, if the screening were scaled up nationally, 124,000 additional patients with diabetes would be referred for care. Notably, the 2012 study was based on fasting blood glucose tests. A national survey in 2008 found that 47 percent of diabetes patients have normal fasting blood glucose and an abnormal oral glucose tolerance test. This means that TB cohorts might actually be found to have twice the prevalence of diabetes if they were screened using an oral glucose tolerance test.

At the same time, a study of screening of diabetes patients for TB in China was published (Lin et al., 2012). Among 11,330 diabetes patients screened, 92 had a positive TB symptom, including 7 with known TB and 48 with newly diagnosed TB. The screening was based on patient-reported data for 5 symptoms: cough for more than 2 weeks, night sweats for 4 weeks or longer, fever for 4 weeks or longer, weight loss for the previous 4 weeks, and any suspicion of active TB to account for extrapulmonary TB.

When comorbid, TB and diabetes must be treated at the same time. Physicians can choose either oral hypoglycemic agents or insulin injections to treat diabetes, though the latter is more frequently recommended. Treatment of diabetes can affect treatment for TB. For example, because the mean plasma concentration of rifampicin is lower in patients with diabetes, exposure to rifampicin is reduced by as much as 53 percent in these patients compared with nondiabetic controls (Nijland et al., 2006). Such pharma-

[6] This section is based on the presentation by Duan Hongfei and Chu Naihui, Beijing Chest Hospital, Capital Medical University.

cokinetic differences may lead to easier acquisition of drug resistance and may explain the lower bacteriological response in diabetic patients with TB, Hongfei observed.

Some studies have found that TB patients with diabetes have more symptoms than those without diabetes, including cough, hemoptysis, dyspnea, fever, night sweats, and weight loss (Alisjahbana et al., 2007). There are also conflicting findings from studies evaluating whether sputum smear positivity is more frequent in diabetes than in nondiabetes. Although some studies have found a greater frequency in diabetes, Alisjahbana and colleagues (2007) found that smear positivity is nearly the same as that in nondiabetes. Hongfei suggested that the discrepancy is probably related to the frequency of cavities in the nondiabetes group, which has a close relationship with smear positivity.

Another influence of diabetes on TB is sputum conversion. Although bacillary protein may be higher at presentation in diabetic compared with nondiabetic patients, leading to modestly longer times to conversion, rates of conversion are similar in both groups by 2 to 3 months of treatment.

Finally, the combination of diabetes and TB may lead to a higher relapse rate and increased risk of death. A study from Egypt found that diabetes conferred a 3.9 times greater risk of treatment failure in patients (Morsy et al., 2003). In Indonesia, a 6-month sputum culture was positive in 22 percent of TB patients with diabetes and in 6.9 percent of controls (Alisjahbana et al., 2007). In the United States, diabetic patients with pulmonary TB have shown a sixfold increased risk of death compared with nondiabetic patients (Oursler et al., 2002). However, whether increased time to culture conversion in patients leads to a higher risk of relapse has not been adequately studied (Dooley et al., 2009).

5

Experiences with MDR TB in Other Countries

Key Messages[a]

- An intensive program of treatment for MDR TB in prisons in Tomsk Oblast cured more than 80 percent of cases, and mortality rates in Tomsk are now half those in the rest of Russia.
- A community-based treatment program in KwaZulu-Natal province cured more than half of MDR TB patients despite major weaknesses in the health care system.
- A community-based model with a hospital/health center component and a home-based component cured more than 70 percent of MDR TB cases in Cambodia and was so successful that it has been replicated in Ethiopia.

[a] Identified by individual speakers.

Three speakers at the workshop provided descriptions of experiences in addressing MDR TB in countries other than China. (Specific issues are discussed in detail in the following chapters in the context of pediatric populations, infection control, rapid diagnosis, treatment across the spectrum of drug resistance, and SLDs.) In all the countries discussed—Cambodia, Ethiopia, Russia, and South Africa—intensive treatment programs based on rapid diagnosis and tailored regimens produced impressive cure rates while overcoming serious obstacles to the delivery of care.

MDR TB IN THE RUSSIAN FEDERATION[1]

Russia has a very complex health care system. Following the collapse of the Soviet Union, the poverty rate in the Russian Federation rose dramatically. Depending on the measure used, somewhere between 35 and 60 percent of the population was living in poverty.

As unemployment rose throughout the 1990s, rates of TB rose as well, from a low of 34 per 100,000 in 1991 to a high of 90 per 100,000 in 2000. Russia also shares with the United States the distinction of having some of the highest rates of incarceration in the world, at close to 700 per 100,000 citizens, and the rate of incarceration in a country tracks with its TB incidence (Stuckler et al., 2008).

The cure rates from WHO's DOTS approach in Russia were very low, observed Salmaan Keshavjee, Harvard Medical School. Instead of the 90+ percent that one would expect in a population of people where drugs were effective, cure rates were in the 60s, and as time went on, the cure rates for the DOTS regimen continued to decline. At the same time, the rate of MDR TB increased—from 6.7 percent in 1999 to 14.4 percent in 2010 among new cases of TB and from 10 percent to 30 percent among all cases of TB.[2]

The spread of MDR TB in Russia had several causes. The prevalence of drug resistance was already high; MDR TB was spreading in the air; HIV infections were increasing; incarceration rates were high; and patients were being treated in hospitals, leading to nosocomial transmission, especially during the intensive phase of treatment. In addition, the pharmaceutical supply systems had broken down, so drug supplies were limited, and drug regimens were inadequate; outpatient systems for observing therapy and managing side effects were lacking as well. More generally, this was happening in an environment characterized by considerable substance abuse, weakened family structures, and people feeling isolated from their communities and surroundings.

In 1998, Partners In Health began working in Tomsk Oblast at the invitation of the Russian Ministry of Justice and the Open Society Institute, which had a program to combat TB in the oblast's prisons. Tomsk is in western Siberia and has a population of about 1 million spread over a

[1] This section is based on the presentation by Salmaan Keshavjee, Director, Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School.

[2] At the time that DOTS became a global program, international advisors were advising the Russians not to treat MDR TB. In 1996, WHO's Groups at Risk wrote, "MDR TB is too expensive to treat in poor countries; it detracts attention and resources from treating drug-susceptible disease." Later, it also was claimed that "best-practice short-course chemotherapy might even reduce the incidence of MDR TB where it had already become endemic" (Dye et al., 2002).

large area. The incidence of TB in the Tomsk prison sector rose substantially in the 1990s, to a high of more than 7,000 per 100,000. The overall prevalence in prisons was more than 20,000 per 100,000. The percentage of MDR TB among new cases was 28 percent and among retreatment cases was 54 percent.

In the nonincarcerated sector, TB rates also had risen, to more than 100 per 100,000. And for all of Tomsk Oblast—including the prison population, the nonincarcerated population, new cases, and retreatment cases—about 41 percent of TB patients had MDR TB.

Many of these patients were resistant not just to ethambutol, isoniazid, pyrazinamide, rifampicin, and streptomycin but also to SLDs used for TB and other diseases. According to the Tomsk Oblast Tuberculosis Services, 49 percent were resistant to kanamycin, 10 percent to capreomycin, and 54 percent to ethionamide, potentially as a result of cross-resistance with isoniazid. Levels of resistance to cycloserine and fluoroquinolones were low. As a result of these resistance patterns, standardized regimens were not sufficient; individual resistance results were necessary to treat patients properly.

Partners In Health worked with the local TB laboratory services and the Massachusetts State Laboratory Institute to ensure that every patient underwent high-quality DST so that the strain with which they were infected could be characterized and their therapy tailored. While the drug susceptibility tests were pending, patients were placed on an empirical seven-drug regimen. When the test results came back, they were used to tailor an appropriate five-drug regimen. Patients took these drugs twice per day for 18 to 24 months. Almost all experienced side effects, which were managed within the program. Patients also had severe comorbidities, such as diabetes and alcoholism, that could worsen the tolerance of medication. Managing side effects is particularly important, Keshavjee emphasized, because it can greatly reduce the rates of default from a treatment program.

Among the first cohort of 244 patients, 45 percent had spent time in prison. Forty-two percent had body mass indexes (BMIs) lower than 18.5. About 50 percent had problems of substance abuse. And two-thirds had cavitary and bilateral disease, so their disease was advanced.

The Partners In Health and Tomsk physicians, assisted early on by the British humanitarian agency MERLIN and later by the Russian Red Cross, worked closely together, focused on ensuring that every patient finished treatment and had the best possible outcome by seeking programmatic solutions to overcome barriers to care. Solutions included improvements to facilities to strengthen infection control, transportation assistance for patients and health workers, a greater choice of treatment sites, and the provision of food assistance. For example, patients could receive both treatment and food at TB hospitals, outpatient hospitals, TB dispensaries, rural

TB offices, and doctors' clinics, as well as during home visits. Patients also received social assistance, such as psychological support, help with government services, clothing in the winter, and help with job searches. These incentives for patients were part of a comprehensive package of medical and social assistance.

Among the prisoners in the first cohort of patients, the cure rate for MDR TB cases was approximately 81 percent, with 12 percent defaulting, 4 percent failing treatment, and 3 percent dying. TB mortality in the Tomsk prison system declined from 384 per 100,000 in 1999 to essentially zero, and it has remained very low (Figure 5-1). For the prison and nonincarcerated population combined, the cure rate was 77 percent, with approximately 5 percent dying. Even among the 29 XDR TB cases in the first cohort, the cure rate was about 48 percent.

In the second cohort, however, the cure rates were not as high, and the default rates were higher. Analysis revealed that rapid expansion of the program had not been matched by building the infrastructure necessary to deal with patients who needed extra levels of care. The solution was to develop a system of patient accompaniment focused on providing care for those at higher risk of default—a "sputnik" (or "fellow traveler") in Russian. A nurse was trained to look after five to seven patients, with responsibility for ascertaining how to get these patients to adhere to a

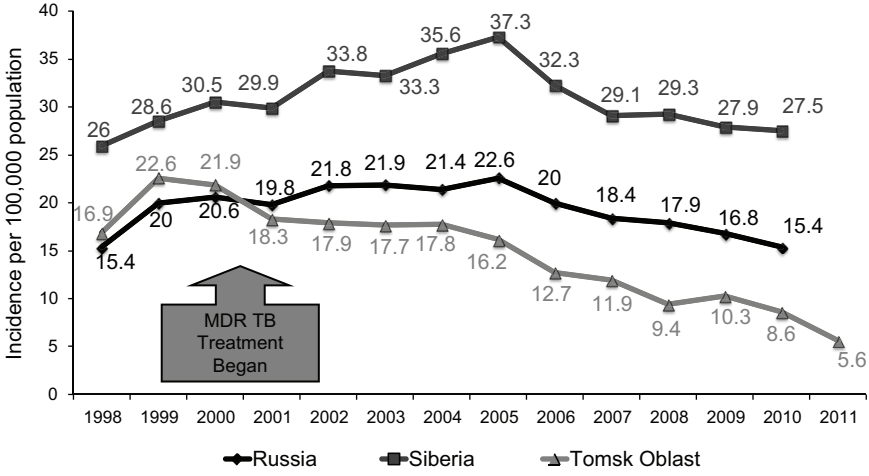

FIGURE 5-1 Comparison of TB mortality in the Russian Federation, Siberia, and Tomsk Oblast (per 100,000 population).
SOURCE: Keshavjee, 2013. Presentation at the IOM workshop on the Global Crisis of Drug-Resistant Tuberculosis and the Leadership of the BRICS Countries: Challenges and Opportunities.

treatment regimen. Patients who defaulted on their treatment were recommended to the sputnik program. This program combined a personal connection to patients, in that nurses would know where and how to reach them, with rigorous management of adverse events, so that patients were comfortable taking their medicines. More important, it shifted the burden of nonadherence from the patient to the program, calling for sound programmatic interventions.

Among the 51 patients who entered the sputnik program between December 2006 and November 2008, adherence was 80 percent for 5 patients who restarted a new treatment course and rose from 52 to 81 percent for the 46 patients who were continuing previous treatment. The cure rate was 64 percent, with 17 percent defaulting. An additional 7.5 percent who were transferred out because of arrests were eventually cured outside of the program. Keshavjee characterized these results as a "reasonably good" cure rate. The cost of the program was somewhere between $500 and $600 a year—"a good value for a program that prevents further transmission of drug-resistant strains of TB and death."

Among the lessons learned from experiences in Tomsk is that transmission can be interrupted, but ways must be found to deliver care to all patients. Tomsk received support from the Global Fund in 2004, which made it possible to treat all of the patients with MDR TB. That same year, MDR TB cases as a proportion of all TB in Tomsk started declining. Building up delivery mechanisms in the ambulatory sector—both facility- and home-based treatment—allowed large numbers of patients to be treated.

TB prevalence in Tomsk has fallen below the overall rates for the Russian Federation, and mortality rates are now one-third of what they are in the rest of the country. Keshavjee emphasized, in conclusion, that programs to treat DR TB can benefit TB programs in general and should not be seen as competing with those programs.

COMMUNITY-BASED CARE IN SOUTH AFRICA[3]

Among the 11 districts in KwaZulu-Natal province, the rate of XDR TB in the district that includes Tugela Ferry was 10 times the rate in any other district, with more than 50 percent of MDR TB cases being XDR, said Kristina Wallengren, K-RITH, University of KwaZulu-Natal, and THINK. Furthermore, the prevalence of MDR was very high, at 30 MDR TB cases per 100,000 population, with the actual number likely to be at least twice as large because of sampling deficiencies.

[3] This section is based on the presentation by Kristina Wallengren, Clinical Advisor, K-RITH, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal; and Chief Executive Officer, THINK.

In 2007, the only MDR TB treatment available in the province was through King George V Hospital, which had 160 beds. Treatment guidelines at the time called for patients to be hospitalized during the 6 months of intensive treatment. With at least 3,000 MDR TB cases in the province every year, capacity was obviously far too low. The hospital increased the turnover of patients, causing more patients to be discharged from the hospital while they were still infectious.

Once discharged, patients were treated in their own communities, in clinics where health care providers had no training in MDR TB treatment or its side effects. In addition, patients were expected to return to the central hospital once a month to collect their medication for the 2 years of total treatment, at times from distances of several hundred kilometers.

Conditions in both central and local hospitals were suboptimal for the burden. There were no isolation facilities, so MDR and XDR TB patients in the hospitals were kept in the same wards, and N95 respirators were not worn.

Under the circumstances, community-based treatment was the only option. The South African Department of Health was wary of having MDR and XDR TB patients treated in their homes because of the possibility of household transmission. However, without a feasible alternative and with the acknowledgment of WHO, the South African Department of Health decided to pilot community-based treatment in four pilot sites in KwaZulu-Natal. The program, carried out with no external funding, was based on the Partners In Health experience in Peru. Each of the four sites had a local hospital with a few beds dedicated to MDR TB cases where patients stayed only if and as long as necessary to stabilize treatment. Other patients started their MDR TB treatment without spending a single day in the hospital.

The best combination, Wallengren said, was to have patients spend 1 or 2 weeks in the hospital. During this time, social workers could visit their homes to see if they had a stable food source and an environment conducive to supporting MDR TB treatment. This period also provided an opportunity to educate patients and their families about the importance of adhering to treatment and about how to respond to side effects.

During the 6 months of intensive treatment, an injection team consisting of a driver and a nurse visited the homes of patients 5 days per week to give the injectable medication kanamycin. Patients who lived close to the clinic went there daily to receive their injections. Patients saw their doctors monthly to review the continued treatment.

In an evaluation of the community-based versus the hospital-based treatment, data from 1,549 MDR TB patients who were followed for 2 years showed that about 51 percent of the patients in the four community-based sites had been cured, compared with 34 percent in the centralized, hospital-based setting. Patients in the community also culture converted much earlier

than patients in the hospital-based setting. More patients in the centralized hospital had previous TB or MDR TB as compared with the decentralized cohort, and the latter patients were more likely to be smear positive at diagnosis. Fifty-four percent of patients in the hospital-based setting had a successful outcome compared with 60 percent in the decentralized sites.[4] However, there was great variation across the four community-based sites, among which successful treatment outcomes ranged from 52 to 72 percent. Other predictors of success were being female; being older than 30; and, for the more than 70 percent of patients in the study who were HIV positive, being on antiretroviral medications.

A second evaluation looked at the performance of the health care system and how it affected the outcomes of MDR TB treatment (Loveday et al., 2013). The evaluation examined the context, the intervention, the mechanism, and the output for health system delivery. According to the evaluation, the four pilot decentralized sites showed substantial differences. The cure rates at the four sites ranged from 46 to 62 percent, and death and default rates also differed significantly. Health outcomes closely tracked the performance scores of the four sites. The factors affecting these differences included ownership of the MDR TB problem at both the district and facility levels, the stability of service (including how long doctors and nurses remained at a site), the integration of services such as TB care and HIV treatment, the availability of drugs, and the quality of care.

Wallengren grounded these statistics in the experiences of a representative patient. During some months the patient was able to receive complete treatment, but in other months treatment was compromised by such factors as bad weather, stock-outs of drugs, strikes of health care workers, and lost medical records (Figure 5-2). In such cases, "it's not the patients who are unwilling to take the treatment or defaulting," said Wallengren. "It's the health system that is failing them."

Wallengren ended on a positive note by observing that in the best-performing pilot site for community-based treatment, treatment success was achieved in more than 70 percent of cases, with 62 percent being cured, in a population where the HIV positive rate was high. She termed these results "phenomenal." Furthermore, the program has been so successful that it has been expanded to six sites in KwaZulu-Natal, and Wallengren and her colleagues have been developing training materials so the program can be rolled out much more widely.

[4] Not all patients with a successful treatment outcome could be deemed a "treatment success." Treatment success is defined as having completed treatment and being identified as cured based on five consecutive culture-negative samples collected at least 30 days apart in the final 12 months of treatment (WHO, 2008).

FIGURE 5-2 Many factors have compromised MDR TB treatment for a typical patient in KwaZulu-Natal province.
NOTE: ART, antiretroviral treatment.
SOURCE: Loveday et al., 2013. Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union.

DIRECT COLLABORATION IN CAMBODIA AND ETHIOPIA[5]

After the Cambodian genocide of the 1970s, more than a million refugees fled to refugee camps on the Thai-Cambodian border. Because of the social disruption within the country, there had been no TB treatment since before 1975, and there was no TB program in place among the emergency interventions implemented in the refugee camps on the Thai-Cambodian border. In the 1980s, a TB program was developed by the American Refugee Committee, which used commonsense interventions such as providing food to patients and making use of patient supporters, often family members, who could accompany patients through therapy. This program served as the first demonstration of treatment of TB patients in a war zone and was one of the earliest demonstrations of successful DOTS.[6] By the time the border camps closed down in 1993, about 10,000 people had been cured.

In 1994, drawing on the success of the earlier program, the Cambodian Health Committee developed a novel community-based approach to TB and later to AIDS treatment, said Anne E. Goldfeld, Professor of Medicine, Harvard Medical School; and Co-Founder, Global Health Committee (GHC) (a nongovernmental organization [NGO] that has worked in Cambodia as the Cambodian Health Committee since 1994 and is based in the United States at Harvard Medical School). Working in one of the poorest parts of Cambodia, where TB prevalence was an estimated 700 cases per 100,000, the program had cured more than 32,000 people through December 2012. Its community DOTS approach has been scaled up to the entire country of 15 million people and is a major reason why new cases have plummeted in Cambodia—recently recognized by WHO as a global achievement.

As part of this program, the Cambodian Health Committee developed an MDR TB treatment program in 2006 based on the same community-based strategies, with a strong emphasis on case finding. The program uses a community-based model with hospital/health center and home-based components. Training, national guidelines, monitoring of the quality of services, active case finding, and strengthening of the national system are other components of the program. About one-quarter of the 282 patients began treatment at home, while the others were hospitalized for at least 1 month.

[5] This section is based on the presentation by Anne E. Goldfeld, Professor of Medicine, Harvard Medical School; and Co-Founder, Global Health Committee (GHC).

[6] DOTS is a WHO TB control strategy used widely throughout the world. The five elements of DOTS are (1) political commitment with increased and sustained financing; (2) case detection through quality-assured bacteriology; (3) standardized treatment, with supervision and patient support; (4) an effective drug supply and management system; and (5) monitoring and evaluation system and impact measurement. For more information, see http://www.who.int/tb/dots/en (accessed August 16, 2013).

For those initiating at home, treatment supporters and health center nurses came to patients' homes to give injections on a daily basis, and combined teams from the Cambodian Health Committee and Ministry of Health made monthly home visits for follow-up, management of side effects, and monitoring. Of the MDR TB patients treated from 2006 through 2010, 70 percent were cured or completed therapy, and less than 8 and 20 percent defaulted or died, respectively.

In 2008, the Cambodian Health Committee began a program in Ethiopia, which, like Cambodia, is mostly rural and very poor, has been affected by conflict, and has a high TB burden. A 2008 survey estimated that about 6,000 new MDR TB cases appeared each year in Ethiopia, yet no program was in place to treat these patients. Training for the Ethiopian MDR TB program took place both in Ethiopia and in Cambodia in 2008, but the program initially was limited because of a lack of availability of SLDs, the absence of an isolation ward at the centralized pulmonary hospital, human resource limitations, only partial laboratory testing, and no outpatient system. The first cohort of patients was admitted to St. Peter's Hospital in February 2009, in an isolation ward that was being reserved for bird flu and was completely empty. Supplies of SLDs made available through private donations from the Jolie-Pitt Foundation and through a drug donation from Eli Lilly and Company ("Eli Lilly") were used until previously promised SLDs from the Global Drug Facility (GDF) gradually arrived over the course of that year. By the end of 2010, a pilot for outpatient treatment was in place, the program had been expanded to northern Ethiopia, and almost 160 patients were being treated for MDR TB.

As of the time of the workshop, in January 2013, 631 patients had been initiated on MDR TB therapy, 107 of whom had been cured or completed treatment, with another 446 on active treatment. Fifty-eight patients had died, and just 10 had had their treatment interrupted or defaulted.

The key to success in Ethiopia, as in Cambodia, has been providing multisectoral support to help patients, said Goldfeld. For outpatients and patients being treated in the community, intensive monitoring, monthly home visits, nutritional support, and social support, including a transportation allowance for returning to the hospital or clinic, are all part of the comprehensive package.

The expansion of the program from Cambodia to Ethiopia represents a south-to-south transfer of an integrated hospital-based and community-based treatment program. It demonstrates that rapid scale-up of MDR TB treatment is possible and effective, said Goldfeld. However, the program continues to face challenges, including a lack of laboratory capacity; the need for funding from international donors; and XDR TB, which remains very expensive to treat in Ethiopia.

6

Drug-Resistant Tuberculosis in Pediatric Populations

Key Messages[a]

- The burden of DR TB in children, the number of children being treated, and the gaps in delivering both treatment and prevention to children are unknown.
- Children can act as sentinels for DR TB, helping countries improve diagnosis and treatment while identifying gaps in knowledge.
- Timely detection and proper treatment of the disease in adults are crucial for protecting children from infection.
- When children are treated with regimens tailored to the susceptibility profile of their strain or of the strain of the most likely source case, they have excellent outcomes.
- Better treatment of TB in children requires new tests and diagnostic tools and more and better drugs that are available in pediatric formulations.

[a] Identified by individual speakers.

Four speakers at the workshop looked specifically at the issue of DR TB in children. Pediatric DR TB is a silent epidemic, they said, and is often overlooked in policy responses. But it reflects the broader spread of MDR TB and offers valuable lessons in how to prevent and treat the disease.

CHILDREN AS SENTINELS FOR TRANSMISSION AND POLICY RESPONSE[1]

"We simply do not know what the disease burden of drug-resistant TB is in children or how it varies across the globe," said Mercedes C. Becerra, Associate Professor, Department of Global Health and Social Medicine, Harvard Medical School. Although HIV specialists have estimated the burden of HIV disease in children, the number of children being treated, and the gaps in delivering both treatment and prevention to children, "we have not generated these estimates at all" for DR TB.

Most current data represent TB cases in adults who have been diagnosed using smear microscopy tests. But because children often have forms of TB that are not detected by a smear test, the existing data are a poor gauge of the extent of pediatric TB cases and the success of treatment. Children typically have a lower bacillary load than adults, they are more likely to develop extrapulmonary forms of the disease, and obtaining testable samples from them is difficult. "Together, this is the perfect recipe for making children invisible," Becerra said.

Recent attempts to describe the pediatric TB burden produced estimates of 500,000 cases per year, but many TB specialists believe that the actual number could be at least twice as high. HIV treatment has been supported by clear estimates showing the need for treatment and global advocacy efforts, but that has not been the case for pediatric TB. The recommended design for national TB surveys excludes anyone under age 15, and children made up less than 2 percent of the more than 300,000 patients included in the Global Drug-Resistant Surveillance Project Surveys (Zignol et al., 2013). "We literally have no sense of where we are and how far we need to go to meet the needs of this vulnerable population across the globe," Becerra said. "The situation is frustrating for us, and it is deadly for children."

Children with DR TB can act as sentinels for the disease, she explained. Children progress more quickly than adults through the stages of the disease, which means they reflect recent transmission and make it easier to identify a source patient. Childhood TB cases, if reported, could help countries progress in diagnosis and treatment of all TB while also identifying gaps in treatment and knowledge.

In the past 4 years, 4 reports of XDR TB in 1 or more children were published in Greece, Peru, South Africa, and the United States, respectively, and 1 each in Beijing and Mumbai, said Becerra, and more than 10 groups in the past 10 years have reported treating children for MDR TB. Thus, the

[1] This section is based on the presentation by Mercedes C. Becerra, Associate Professor, Department of Global Health and Social Medicine, Harvard Medical School.

problem is not limited to a particular part of the world. "These are surely just the tip of the iceberg of undetected resistant TB in children in all of these places."

Similarly, Becerra and her colleagues found that reports of resistance to isoniazid, either alone or in combination with other drugs, are widespread in children. In more than half of the studies they reviewed, isoniazid resistance was more than 5 percent, suggesting that many children will not benefit from empirical treatments that rely on isoniazid (Yuen et al., 2013). However, when children are treated with regimens tailored to the susceptibility profile of their strain or the strain of the most likely source case, they have excellent outcomes. More than 80 percent of those who have accessed complete regimens have been cured.

At the fourth workshop in this series, held in New Delhi, India, in 2011, the idea emerged of forming a virtual network of collaborators, including researchers, caregivers, and advocates, who would work together with the goal of ending childhood deaths from DR TB. The resulting Sentinel Project on Pediatric Drug-Resistant Tuberculosis[2] now includes more than 250 individuals from more than 50 countries who are working to raise the visibility of this vulnerable population, share knowledge and best practices, and formulate a scientific agenda that gives priority to children. Since forming, one task force has gathered short stories detailing the experiences of almost 70 children with DR TB in more than 30 countries ("Being Brave: Stories of Children with Drug-Resistant Tuberculosis," 2012; "We Can Heal: Prevention, Diagnosis, Treatment, Care, and Support: Addressing Drug-Resistant Tuberculosis in Children," 2013). Another task force, made up of providers with extensive experience treating drug-resistant pediatric TB, has written a 50-page practical field handbook (*Management of Drug-Resistant Tuberculosis in Children: A Field Guide*, 2012) based on state-of-the-art knowledge in the field (Seddon et al., 2012b). The next steps for the network, Becerra said, are to articulate a scientific agenda and initiate multisite research projects that can identify targets for monitoring.

Children with DR TB also can serve as sentinels for policy responses, said Becerra. Where DR TB occurs in adults, children also are likely to be exposed. For example, children living with DR TB patients in Peru had 30 times the risk of disease of the general pediatric population. Screening of household contacts is known to be a best practice in TB care, and if it were performed as a standard practice, could contribute to diagnosis of more pediatric cases. "If we want to find children with drug-resistant TB, we have to look for them where they live," said Becerra.

Becerra proposed a way of beginning to estimate the number of children at risk. Estimates of patients with DR TB, she said, can be multiplied

[2] See http://www.sentinel-project.org (accessed April 15, 2013).

by the average number of children in those households, yielding an absolute number of children that need to be evaluated. That target number comes to nearly 800,000 in a single year, based on recent WHO data. Using an average risk statistic, Becerra calculated the number of children expected to already be sick as 3.4 percent of the total (Fox et al., 2013)—an absolute number of more than 25,000 children currently needing treatment. This approach, Becerra explained, can begin to focus attention on the treatment gap and what can be done in the short term to serve the pediatric population.

Finally, better treatment of TB in children requires new tests and diagnostic tools and more and better drugs that are available in pediatric formulations. A framework that highlights basic treatment targets can be used as scaffolding for a scientific agenda that makes children a priority and can provide benchmarks for refining treatment and delivery strategies so as to increase the number of children treated.

PEDIATRIC DRUG-RESISTANT TB IN CHINA[3]

Tao Li, Attending Physician, and Assistant Director, Department of Tuberculosis, Shanghai Public Health Clinical Center, Fudan University, began his presentation with the story of 4-year-old boy who has spent virtually his entire life in the hospital with DR TB. Pediatric TB has been neglected, Tao Li said, pointing out that the first WHO report, including estimates of children's TB—490,000 new cases and 64,000 deaths per year—was published in 2012. In China, TB infection rates among children were last updated 12 years ago, showing a rate of 25 percent. According to the China CDC, 1,996 cases of new smear-positive TB occurred in children in 2004.

From 1996 to 2006, the number of pediatric TB cases increased gradually at Beijing Children's Hospital. However, the number increased rapidly in Shanghai, where the Shanghai Public Health Clinical Center, the only designated hospital for children's TB, draws children from all over the country.

For a doctor, Tao Li explained, the biggest challenge posed by children's TB is diagnosis. Most children have TB that is difficult to diagnose with a smear culture, and good samples are challenging to collect. In addition, diagnosing extrapulmonary TB requires special services that often cannot be provided in general hospitals.

Among 211 cases of children's TB at the Shanghai center admitted between June 2010 and December 2011, a retrospective study showed extensive involvement of the lymphatic system in 48 percent of patients and

[3] This section is based on the presentation by Tao Li, Attending Physician, and Assistant Director, Department of Tuberculosis, Shanghai Public Health Clinical Center, Fudan University.

a low coinfection rate with HIV of only 1.6 percent. Only 6.6 percent of the children had a history of close contact with TB patients. Two-thirds were susceptible to all four FLDs, one-third were resistant to at least one FLD, and 5 percent had MDR TB. Only one child had an unfavorable outcome.

Performing multiple tests increases the chances that a child will be diagnosed and treated effectively. In that regard, a multicenter, prospective cohort study showed that collecting a variety of specimens increases the chances of an accurate diagnosis. Specimen types included cerebrospinal fluid, pleural fluid, and lymph node aspirates.

Children are the future, Tao Li concluded, and knowing that those with DR TB have favorable outcomes when treated is comforting. For example, the child he described at the beginning of his talk has recently shown improvement. Persistence in diagnosis and treatment will pay off in the long run, said Tao Li.

DRUG-RESISTANT TB MENINGITIS IN CHILDREN[4]

Tuberculous meningitis (TBM), which is more common in children than in adults, is the most severe type of TB, noted Huimin Li, who presented a talk prepared by Shunying Zhao, Beijing Children's Hospital. Diagnosis of TBM in children is difficult and often delayed, and about 80 percent of children with stage II and III TBM develop neurologic sequelae.

TB in children is usually paucibacillary, and microbiologic diagnosis can be made in only 20 to 40 percent of cases. Furthermore, many hospitals, including Beijing Children's Hospital, cannot perform DST. As a result, the diagnosis of MDR TB in children is often made presumptively. According to Huimin Li, MDR TB therapy should be considered if a patient has a history of TB, has an MDR TB contact, or has a poor clinical response to first-line TB therapy within 2 weeks despite adequate adherence to treatment.

Treatment of drug-resistant TBM should be based on the results of DST, testing of the source case if possible, the prevailing patterns of drug-resistant strains in the region, or the experience of practitioners. The recommended treatment regimen is the combination of at least four drugs to which TBM is likely to be susceptible.

Although data on drug-resistant TBM in children are limited, Huimin Li presented the results of two earlier studies. In the first study (Padayatchi et al., 2006), eight children from South Africa were studied between 1992 and 2003, six of whom were HIV positive and two of whom were not. Only one of these children survived. In the second study (Seddon et al., 2012a), 16 of 123 children with TBM from South Africa, studied from

[4] This section is based on the presentation by Huimin Li and Shunying Zhao, Beijing Children's Hospital.

January 2003 to April 2009, had any form of drug resistance, and 4 percent (5 of 123) had MDR TB. MDR TB was strongly associated with both unfavorable outcomes and death. No differences were found between the outcomes of children with isoniazid-monoresistant TBM and children with drug-susceptible TBM.

Huimin Li presented clinical data from 210 children with TBM in Beijing Children's Hospital from January 2002 to June 2010. These children had a high incidence of possible drug resistance, and most were at stage II or III of the disease. With treatment, 80.5 percent improved, 18.1 percent had an exacerbation of their condition or no improvement, and three died.

Huimin Li emphasized that it is essential to perform drug resistance testing in children with TBM in the future, including DST and tests using molecular biology methods, to rapidly diagnose drug resistance. Results can help determine the choice of TB drugs and improve the prognosis for these patients.

Huimin Li also presented the results of treating children with MDR TBM with linezolid, which has high in vitro antibacterial activity against TB. Research in adults has shown that linezolid is effective against MDR TB but also has a high incidence of serious adverse events, including neuropathies and bone marrow suppression. Among 10 children with clinically diagnosed drug-resistant TBM treated with linezolid for 1 to 3 months, none had adverse events, 9 improved, and 1 changed to a different treatment. Future research is needed to determine the best treatment regimen for linezolid, Huimin Li concluded, and to further assess its efficacy and safety in children with MDR TBM. Nonetheless, these results indicate that linezolid has better efficacy and safety in treating drug-resistant TBM in children than in adults.

PEDIATRIC MDR AND XDR TB IN THE RUSSIAN FEDERATION AND OTHER COUNTRIES OF THE FORMER SOVIET UNION[5]

TB is challenging to Russian pulmonologists, explained Valentina Aksenova, Head, Children and Adolescents Department, Research Institute of Physiopulmonology of the First Sechenov Moscow State Medical University; and Chief Freelance Expert Pediatrician-Physiologist of the Russian Health Ministry. This is the case for many reasons, including late detection, undiagnosed cases of extrapulmonary TB, drug resistance, and coinfection with HIV. In Russia, 100 of every 100,000 adults and 16 of every 100,000 children have TB. Morbidity is highest in those aged 25 to 34.

[5] This section is based on the presentation by Valentina Aksenova, Head, Children and Adolescents Department, Research Institute of Physiopulmonology of the First Sechenov Moscow State Medical University; and Chief Freelance Expert Pediatrician-Physiologist of the Russian Health Ministry.

Approximately 60 percent of the Russian population has regular occupational health exams, which help increase the likelihood of diagnosing TB cases. Of those diagnosed, 44.4 percent have bacterial excretion, 47.3 percent have degraded lung tissue, and 10.7 percent have MDR TB.

Pulmonologists who treat children and adults face similar challenges, but particular challenges are posed by pediatric TB. It is more difficult to diagnose than TB in adults, so it is detected in more advanced stages, and inefficient infection control measures are in place. In 2011, 234,000 children in Russia were infected, 2,818 were diagnosed with active TB, and 1,437 were diagnosed with latent forms of the disease.

Drug resistance is found in more than 50 percent of pediatric cases, Aksenova added. TB is often found in the lymph glands of children, and teenagers frequently present with complex forms of secondary TB.

Aksenova described a study of 65 children with DR TB and a control group of 95 children with drug-susceptible TB (Aksenova, 2013). The study found that contact with someone who had active TB was a primary risk factor for the development of drug resistance in children, along with an interrupted course of chemoprophylaxis.

Analysis of the forms of drug resistance in pediatric TB showed generalized resistance to FLDs in 89 percent of children. Forty percent were resistant to kanamycin, and 38.5 percent had MDR TB. One child in the group was resistant to all drugs. In the study, 9.2 percent of children with drug-resistant forms of the disease were resistant to a single drug, and 52 percent had polyresistance.

Children with DR TB were 1.8 times more likely to have acute onset of the disease and 2.2 times more likely to have significant symptoms, Aksenova said, while children from the control group were three times as likely to have multiple symptoms at the outset. Accelerated disease was typical for children with drug-resistant strains but was seen less often in those in the control group.

The type of treatment needs to be based on the resistance, Aksenova said. In addition, children who have contact with patients with MDR TB should take preventive therapy with two anti-TB drugs for 6 months, which is compulsory in pediatric sanatoria in Russia.

Prevention is also key. Timely detection and proper treatment of the disease in adults are crucial for protecting children from infection. For chronic forms of TB, reliable isolation of children from the patient is preferable. Better continuity between adult and pediatric services could contribute to tracking and preventing the spread of infection.

Recommendations for preventing transmission should be distributed to patients who have contact with children, Aksenova said. Refusal of treatment and lack of isolation are challenges for doctors, and outreach is

necessary to explain the value of preventive care, regular exams, and proper treatment protocols.

Improving the socioeconomic situation, providing effective drugs, using modern treatment methods, and ensuring that patients adhere to their treatment would help control the spread of resistant TB strains in Russia. Russia has both a federal target program for preventing socially significant diseases and a subprogram for urgent measures to address TB.

Aksenova concluded her presentation with a quote from Lucica Ditiu, executive secretary of the Stop TB Partnership: "Every day TB kills 200 children. And this is despite the fact that the therapy which prevents disease in children is less than 3 cents a day, and treatment of the disease costs 50 cents a day. But before we can provide prevention and treatment, we have to find those at risk of TB, and this is possible only when governments, civil society and the private sector work together."

7

Global Perspectives on Transmission and Infection Control

Key Messages[a]

- Undergirding efforts at effective infection control is a comprehensive approach that includes redesigning health care facilities and implementing rapid diagnosis and early treatment of DR TB.
- The focus of infection control in China has been on engineering controls and personal protective equipment as opposed to administrative and managerial practices.
- The spread of TB among health care workers points to the need for continued strengthening of infection control programs.
- Although infection control programs can be expensive, they are much less costly than treating people with DR TB.

[a] Identified by individual speakers.

Participants in the workshop focused substantial attention on the potential for MDR TB to spread from person to person. Speakers discussed general findings on the transmissibility of DR TB and implications for infection control, as well as specific issues in the context of individual countries, particularly relating to the need to protect health care workers from infection. Many speakers and participants recognized in their remarks a common theme echoed throughout the workshop, that MDR TB is acquired more often by transmission than by incomplete or inappropriate treatment.

THE VALUE OF GENOTYPE MAPPING[1]

In the past, most of the emphasis on DR TB has been on resistance acquired through incomplete or inappropriate treatment, said Neel R. Gandhi, Associate Professor, Departments of Epidemiology, Global Health, and Medicine, Rollins School of Public Health, Emory University. As a result, TB programs have concentrated on understanding how best to keep individuals from developing resistance through multidrug therapy, directly observed therapy, and other adherence measures. However, individuals also can become infected with DR TB through transmission from another person. This primary, or transmitted, resistance can occur even in individuals who have never been on anti-TB therapy.

The interventions used to treat acquired and transmitted resistance are very different, Gandhi noted. With acquired resistance, the way to prevent additional DR TB is to strengthen the drug-susceptible TB treatment program. With transmitted resistance, transmission needs to be prevented through infection control programs.

In the past, it has commonly been believed that the same mutations that create resistance to medications will exert a fitness cost, making these strains less likely to propagate and generate clinical disease through transmission. According to this perspective, existing drug-resistant strains eventually will die out, and thus the focus should be on ensuring that new drug-resistant strains are not being generated. The advent of genotyping methods in the 1990s enabled a much better understanding of transmission. Genotyping allowed assessment of whether patients had very similar drug-resistant strains, and in those cases one could conclude that transmission likely occurred between them.

Also in the 1990s, high-profile outbreaks in the United States and in Western Europe, and somewhat later in other parts of the world, demonstrated that DR TB strains can be transmitted quite efficiently. These outbreaks of transmitted strains occurred most commonly in congregate settings, such as hospitals. Most TB control programs in hospitals at the time relied on smear microscopy, which cannot reveal drug susceptibility or resistance; the result was delays in diagnosing drug resistance. Delays in performing culture and DST added more time to the process. As a consequence, many patients were not diagnosed as having MDR TB until weeks or months after they had arrived at an institution, during which time many other patients and workers may have been exposed to the disease.

The hospitals where many of these outbreaks occurred had few, if any, infection control measures in place. They tended to have congregate wards

[1] This section is based on the presentation by Neel R. Gandhi, Associate Professor, Departments of Epidemiology, Global Health, and Medicine, Rollins School of Public Health, Emory University.

where a number of people shared the same air space with little ventilation. Even hospitals that had isolation facilities did not use them effectively. Patients were isolated only when a confirmed diagnosis was made, after weeks or months of delay. Isolation rooms also tended to be poorly maintained. Airflow studies in several facilities showed that, instead of having negative pressure to prevent air from the isolation room from spreading elsewhere, many rooms had positive pressure because of poor maintenance of the ventilation systems. When the doors were open, the air from those rooms spread into the hallway and adjacent rooms.

These conditions resulted in significant transmission to health care workers. In many settings, health care workers' tuberculin skin test (TST) conversion rates were on the order of 30 to 60 percent. For many who developed active TB, the strains could be traced back to the outbreak strain.

As knowledge of these problems grew, significant interventions in the United States and Europe turned the tide and reduced the number of DR TB cases. But those lessons were not applied globally. Gandhi showed a picture of the Tugela Ferry, South Africa, hospital TB ward where he has worked for the past 10 years. It has congregate beds with up to 40 patients per ward. When the ward was crowded, the hospital accommodated additional patients by placing mattresses on the floor between the beds—"a scenario for widespread transmission."

From 2005 to 2009, 516 XDR TB cases from this one hospital were diagnosed and culture confirmed. This equates to an incidence of 52 XDR TB cases per 100,000 population in that community—"astounding rates," according to Gandhi. Genotype testing showed that more than 85 percent of these cases could be traced to a single predominant clone. Most of those patients had been exposed to 1 or more infectious XDR TB patients on the hospital's wards, with a mean period of overlap of 18 days.

Further analysis showed that instead of a single, point-source outbreak, the XDR TB epidemic in Tugela Ferry arose as a result of multiple generations of transmission of DR TB strains. It was found that at least 5 generations of XDR TB transmission had occurred over the 2-year period 2005–2007, and other observations point to a similar phenomenon with MDR TB strains. With this mode of transmission, there are circumstances in which the number of DR TB cases can rise exponentially. In 2001, KwaZulu-Natal had only 210 MDR TB cases. By 2007, it had more than 3,000, and the number for 2012 is approximately 4,500, which, Gandhi said, is still likely to be a two- to threefold underestimate. By way of comparison, the United States had fewer than 100 MDR TB cases in a recent year.

Gandhi closed by drawing some general conclusions about genotyping in the context of MDR TB:

- Pooling of genotyping data allows identification of transmission across large geographic areas.
- Epidemiological investigation and network analysis allow better characterization of transmission relationships between clustered cases.
- Clustering can occur not just across cities and states but also across national boundaries. In a study of cases from 19 European countries, as many as 43 percent were clustered across European borders (Devaux et al., 2009). Furthermore, many of these cases actually began in Eastern Europe, Central Asia, or West Africa.
- These findings suggest that transmission is occurring not just in hospital settings but in other settings as well. For example, studies have documented transmission in households (Becerra et al., 2011; Vella et al., 2011).

Studies also have shown that people previously treated for TB who develop DR TB—historically assumed to be a sign of acquired resistance—often are instead being reinfected with drug-resistant strains through transmission. For example, a study in San Francisco looking at patients who developed resistance while on treatment found that 45 percent had an isolate completely different from their susceptible baseline isolate (Small et al., 1993). Li and colleagues (2007) found a reinfection rate of 84 percent in a study in China, and a study in South Africa, in a high-HIV-prevalence setting, found a reinfection rate of 100 percent (Andrews et al., 2007).

Beginning in 2010, WHO began estimating transmitted versus acquired cases differently, with transmitted cases now including both new TB cases and those who relapse after having had successful TB treatment. These new estimates indicate that close to three-quarters of the MDR TB cases that are estimated to arise globally are a result of transmission rather than acquired resistance (WHO, 2010). Similarly, a study released in China in 2012 found a transmission rate for MDR TB of 78 percent (Zhao et al., 2012).

Two decades of experience have definitively demonstrated that transmission plays a significant role in the development of MDR and XDR TB cases, Gandhi said. Halting transmission therefore needs to be a critical element of efforts to address the epidemic of DR TB. To this end, a comprehensive strategy is required that includes the redesign of health care facilities and rapid diagnosis and early treatment of DR TB.

Complementing Gandhi's presentation were remarks by a speaker from China who discussed the characteristics of the hospital system in China and how patients use the system for TB care. This presentation is summarized in Box 7-1.

BOX 7-1
The Hospital System in China[a]

According to Liang Li, Director, Administration Office, Clinical Center on Tuberculosis, China CDC; Vice-Director, Chinese Tuberculosis Society; Chief-Director, Beijing Chest Hospital, China has more than 3,000 TB dispensaries. It also has 203 TB specialty hospitals, to which general hospitals transfer identified TB patients. However, these TB hospitals are unevenly distributed, so that an outbreak in, for example, the western part of China is a much bigger problem than an outbreak where TB hospitals are more numerous.

The TB hospitals in China include a total of 6,000 doctors and 8,000 nurses, according to Li. But they have only about 300 laboratory personnel, which he described as a very small number.

TB dispensaries, or local clinics at the county or district level usually located at the site of the local China CDC, diagnose more than 60 percent of TB patients, with TB hospitals finding another 20 percent and general hospitals finding 15 percent. More than 60 percent of the TB hospitals can conduct DST and culture. However, the fact that less than 20 percent of TB dispensaries can perform these tests is problematic because of the large number of MDR TB patients in China and the large numbers that rely on the dispensary system for diagnosis.

China has eight TB hospitals that have been authorized to perform clinical trials of new drugs and recently established a National TB Clinical Trials Consortium that will involve additional TB hospitals. In addition, TB hospitals have the capacity to conduct basic and clinical research, said Li, such as a recent effort to develop new methods of MDR TB diagnosis.

[a] This box is based on the presentation by Liang Li, Director, Administration Office, Clinical Center on Tuberculosis, China CDC; Vice-Director, Chinese Tuberculosis Society; Chief-Director, Beijing Chest Hospital.

INFECTION CONTROL CHALLENGES FOR HEALTH CARE WORKERS IN CHINA[2]

Chinese hospitals tend to be large and crowded, some having between 500 and 1,000 beds, said Carol Rao, Chief of Epidemiology Section, International Emerging Infections Program, Global Disease Detection, U.S. CDC, China Office. TB cases usually present to village doctors or to gen-

[2] This section is based on the presentation by Carol Rao, Chief of Epidemiology Section, International Emerging Infections Program, Global Disease Detection, U.S. CDC, China Office.

eral hospitals first, rather than specialty TB hospitals. China has national guidelines but no national policies on surveillance monitoring specifically for TB infection control.

Current infection control practices in both TB and general hospitals generally include ultraviolet germicidal irradiation (UVGI). But they do not employ the upper-room shielded ultraviolet (UV) lights used in many countries; rather, they employ unshielded UV lights that are turned on for 10 to 15 minutes after a patient leaves a room to disinfect surfaces and the air and are then turned off before another patient arrives.

TB hospitals also have increasingly established infection control departments, particularly after the SARS epidemic. N95 respirators or gauze masks are issued intermittently to the health care workers, but with little training in their use. The focus of infection control is on engineering controls and personal protective equipment, said Rao, as opposed to administrative and managerial practices.

China CDC and U.S. CDC undertook a joint project to examine the prevalence and incidence of TB infection among Chinese health care workers. At the time of the study, no accurate, representative estimates of TB infection were available for China.[3] The study sought to establish a baseline against which to measure the impact of infection control, thus strengthening the commitment to infection control. The study, conducted in Inner Mongolia, also looked at the knowledge, attitudes, and practices of hospital-based health care workers in 43 health care facilities. For the study, 4,000 people completed the survey questionnaire; 2,000 of these people underwent a chest X-ray and TST; and 1,000 were administered a QFT, despite its not yet being licensed in China. Only 17 percent of participants reported ever having received a TST, and two-thirds of them said they had received the test more than 5 years ago. Among the small number who had been tested, 42 percent said the test result was positive.

In general, said Rao, people knew the right answers to questions on the knowledge, attitudes, and practices survey. They had good knowledge of how TB is transmitted and how transmission is prevented. One notable finding was the mistaken belief that cleaning tables, beds, and floors with bleach would prevent TB transmission, a misconception that was promulgated in Chinese policy documents.

Most participants said they wear a mask when they are working with a TB patient. But when asked what type of mask, only 40 percent said a respirator. Moreover, Rao noted, some may have given this answer because they knew it was correct, even if they did not always wear a respirator.

[3] Previous surveys used TST, because at the time QuantiFERON-TB test (QFT) was not licensed for use in China. Moreover, the tuberculin used in China for testing was a BCG derivative and not the international standard that is used in other countries.

Of the 2,000 people who received a chest X-ray and TST, 2 percent had an X-ray consistent with TB, which, together with other signs of possible TB, led to 102 participants being suspected of having TB. But none of these people were smear-positive, which is the hallmark for diagnosing TB in Inner Mongolia.

Among the 1,000 health care workers who underwent QFT, the rate of positive results was higher in the general hospital where the testing was done than in the TB hospital. The higher prevalence in the general hospital may be the result of sick patients presenting to village doctors or general hospitals before being referred to a TB hospital. Among the risk factors for positive results were several activities associated with work tasks, such as having a coworker with TB, spending more time with patients, and the number of years spent in health care.

A follow-up a year later among the 1,000 workers who underwent QFT revealed that 12.5 percent of those who participated in the follow-up had converted to positive results over the course of the year. Among those who had a follow-up TST, the conversion rate was 9.1 percent, which translated to about 6.7 per 100 person-years. Thus, both the prevalence and incidence of TB infection in health care workers in Inner Mongolia were relatively high.

More studies are needed to measure continuing incidence and to compare these results with community infection rates, which today are unknown in Inner Mongolia, said Rao. Results from such studies could strengthen infection control, guide best practices, and ensure that policies are based on evidence.

INFECTION CONTROL CHALLENGES FOR HEALTH CARE WORKERS IN SOUTH AFRICA[4]

Health care workers are at increased risk of both latent and active TB (Joshi et al., 2006; Menzies et al., 2007). A study of eight public hospitals conducted in eThekwini district in KwaZulu-Natal province, the district where Durban is located, found an incidence of TB of more than 1,000 per 100,000—higher than the national incidence of TB in South Africa (Naidoo and Jinabhai, 2006). Also in Durban, a chart review of patients who had identified themselves as health care workers found that they had a five- to sixfold greater risk of MDR or XDR TB than those who had not identified themselves as health care workers (O'Donnell et al., 2010).

Carrie Tudor, Fogarty Global Health Postdoctoral Fellow, Johns Hopkins School of Nursing, University of North Carolina at Chapel Hill,

[4] This section is based on the presentation by Carrie Tudor, Fogarty Global Health Postdoctoral Fellow, Johns Hopkins School of Nursing, University of North Carolina at Chapel Hill.

has been involved in a study looking at occupational risk factors for TB in KwaZulu-Natal province. In three general hospitals with specialized MDR TB wards, 1,682 health care workers were employed in 2011. After eliminating charts that had inadequate information, just more than 1,400 employee medical records were available. All of the hospitals, which ranged in size from 170 to 280 beds, had occupational health nurses, but only two had nurses who worked full-time. Only one of the occupational health nurses had postgraduate occupational health training, and there were no occupational health and safety officers at any of the hospitals. All the hospitals had full-time infection control nurses.

Each of the hospitals had recommended occupational health and infection control policies and guidelines, although the extent to which these policies and guidelines were observed varied. For example, only one hospital reported receiving good-quality N95 respirators, while the other two reported receiving fake or poor-quality N95 respirators.

In these hospitals, there are no standardized TB screening tools or guidelines for how often health care workers should be screened. In 2010, only 19 percent of the health care workers in these hospitals were screened for TB. Each hospital identified one case of active TB in 2010 through its screening efforts. Many cases were not detected until the health care worker was symptomatic and sought care.

A retrospective cohort analysis of the data collected through employee medical records compared the incidence of TB among those health care workers who worked in a TB ward and those who did not. Based on just more than 1,300 charts that included work location information, a higher percentage of those who worked in TB wards had been diagnosed with TB. But among those with DR TB, none had worked in a TB ward. Also, clinical staff were more likely than nonclinical staff to have DR TB, and those with drug-susceptible TB were more likely to be HIV positive.

Those who work in MDR wards are reportedly screened more frequently than those working in other areas of the hospitals, said Tudor. An infection control assessment of all the wards of all the hospitals revealed that infection control practices in the MDR TB wards were far superior to those in the non-MDR TB wards. Windows were always open, N95s were available and were used, and sputum samples were collected outdoors.

A multilevel mixed model was used to calculate the incidence rate ratios of TB among health care workers in the three hospitals. The incidence of TB among those working in various TB and non-TB wards of the hospitals, including pediatric wards, was higher than the average among the general population of KwaZulu-Natal, as was also the case among those who were HIV positive. Compared with the general population, the incidence rate ratio among health care workers was 1.7 to 2.5 times greater.

The researchers also compared the experiences of a sample of staff

members diagnosed with active TB between January 2006 and December 2010 and controls who worked in the same hospital but did not develop TB. The cases and controls were similar on most characteristics, including duration of employment, but cases were much more likely to be HIV positive. Also, mean household crowding was higher among cases than among controls. A slightly higher percentage of cases than controls had household TB contacts, but the difference was not significant.

The overall study of occupational health medical charts had several limitations, said Tudor:

- The charts were not always complete.
- The use of a self-report questionnaire for the case-control studies may have introduced a social desirability bias if respondents knew what responses the researchers would view in a positive light.
- The case-control study had a small sample size, and TB and HIV status were probably underreported.

An implication of this study is the need to improve regular TB screening of health care workers so as to detect cases more quickly. In addition, effective infection control measures are needed in all wards, not just in TB or MDR TB wards. And all health care workers need to receive HIV counseling and testing, which will require reducing the stigma associated with HIV and TB and alleviating concerns about confidentiality.

Tudor recommended that isoniazid preventive therapy be offered to HIV positive staff, a measure initiated in South Africa in May 2011 through occupational health clinics. HIV positive staff should be reassigned to low-risk areas when possible, although such areas are lacking in some hospitals, and the study results indicate that the MDR TB ward is a relatively safe place to work. Starting HIV positive patients and health care workers on antiretroviral therapy sooner—economics aside—might help protect the workers. Finally, symptom screening of all patients when they are admitted to the hospital for any reason could help protect both patients and workers.

INSTITUTIONAL INFECTION CONTROL IN RUSSIA[5]

Vladimir Oblast is a relatively small region with a population of about 1.5 million in the European part of Russia. Grigory V. Volchenkov, Vladimir Oblast TB Dispensary, Center of Excellence for TB Infection Control, described the region's TB infection control program. This program, which

[5] This section is based on the presentation by Grigory V. Volchenkov, Chief Doctor, Vladimir Oblast TB Dispensary, Center of Excellence for TB Infection Control.

involves both the civil and penitentiary sectors, was launched in 2002 in the wake of joint efforts with the WHO TB control program in the Russian Federation and with U.S. CDC in 1999.

Before the program began, occupational TB infection among health care workers was common. The average active TB notification rate for health care workers in the Vladimir Oblast TB Dispensary was 1,080 cases per 100,000 population in the 10 years before the program began (Volchenkov et al., 2004). The risk of TB among health care workers was 22 times higher than that among the residents of the surrounding area. The cross-transmission of TB and MDR TB among patients also was high (Gelmanova et al., 2007).

In 2001, a 28-year-old anesthesiologist who worked in the bronchoscopy room, where effective risk-reduction measures were lacking, died of TB. This tragic event helped motivate the dispensary to implement effective infection control measures.

In 2003, the dispensary was moved into a former children's hospital in Vladimir. In the old facility, patients were not triaged, and those for whom smear positivity raised suspicion of drug resistance were placed with other patients in rooms that could include 18 beds. Not all staff used gauze masks; there were no upper-room open UVGI fixtures; and open windows were the only form of ventilation.

In the new facility, mechanical ventilation systems were installed in high-risk departments. Patients were separated into low-, medium-, and high-risk zones, with special signage indicating the risks. With the support of U.S. CDC, 160 upper-room UVGI fixtures were installed in the high-risk zones. And a personal respiratory protection program was implemented for high-risk staff.

The new facility housed only patients receiving effective treatment. Patients were separated based on the results of smear and DST, molecular testing not being available at the time. More recently, the facility has implemented GeneXpert devices; there are now five such devices being used for the oblast. Adoption of a diagnostic and treatment protocol using this method has reduced the risk of transmission of DR TB.

The MDR TB ward in the prison sector also was reconstructed to reduce the risk of transmission. With support from the Global Fund, an 80-bed MDR TB ward was constructed for imprisoned patients, with low-, medium-, and high-risk zones. Rooms are mechanically ventilated and have upper-room UVGI.

These interventions reduced the risk of occupational TB to a level lower than the risk of TB among the general population. During the past 4 years, no cases of occupational TB have occurred among the staff in the region overseen by Volchenkov (Figure 7-1).

In light of this success, WHO and U.S. CDC helped organize the

Vladimir Center of Excellence for TB Infection Control, with additional support from the Central TB Research Institute, Moscow. The center provides six to eight courses per year for health care workers, administrators, laboratory managers, chief nurses, engineers, architects, and other professionals. Professionals from almost all the countries of the former Soviet Union have taken these courses, and the center has supported TB infection control programs in many of these countries, as well as elsewhere.

A safe TB control program is no more expensive than a traditional one, said Volchenkov. Reducing the hospitalization rate saves resources, and providing safer conditions for a limited number of infectious cases leaves more resources available for the TB control program.

Volchenkov listed several scientific and practical impacts of the Vladimir project:

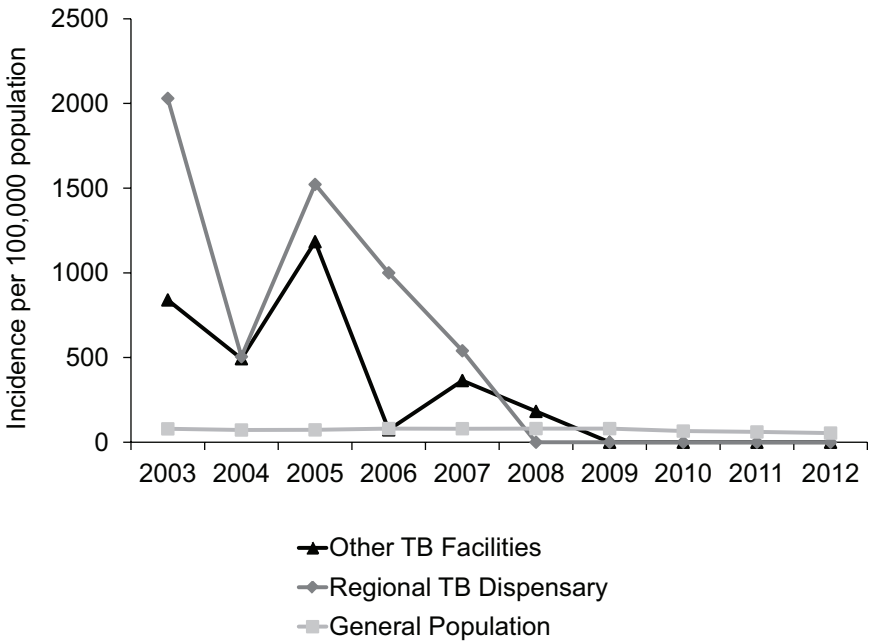

FIGURE 7-1 The incidence of occupational TB infection among health care workers providing TB services in the Vladimir region of Russia fell to zero after an infection control program was implemented.
SOURCE: Volchenkov, 2013. Presentation at the IOM workshop on the Global Crisis of Drug-Resistant Tuberculosis and the Leadership of the BRICS Countries: Challenges and Opportunities.

- Upper-room UVGI fixtures, the first of which in Russia were installed in the Vladimir Oblast TB Dispensary, now are being used throughout the former Soviet Union and have proven to be an inexpensive and effective engineering method for controlling infection.
- Negative-pressure sputum collection booths have been beneficial for countries with a cold climate.
- In-duct UVGI has been implemented to disinfect exhaust air from high-risk areas.
- A study was performed to compare the cost-effectiveness of various engineering controls.
- An inexpensive but effective and sustainable respiratory protection program has been instituted throughout facilities in the region.
- Separate wards for MDR and XDR TB patients and for children were nearing completion in the Vladimir Oblast TB Dispensary at the time of the workshop.
- A well-equipped training laboratory for engineers and architects was built in the dispensary.
- Diagnostic, separation, and treatment algorithms based on rapid molecular diagnostic methods were developed.
- The Vladimir Center of Excellence for TB Infection Control provided support to several countries for the development of national guidelines on TB infection control.

Volchenkov also listed the specific infection control challenges Russia has faced, some of which may apply to other BRICS countries as well:

- A cold climate requires mechanical ventilation in areas with high-risk TB patients.
- Long-term hospitalization with general neglect of administrative measures for TB infection control is common.
- The weak involvement of primary health care services in TB outpatient services can severely limit community-based care for TB patients.
- National guidelines focused only on contact and droplet transmission neglect to cover precautions for airborne transmission.
- Investments in TB infection control lacked prioritization so that, for example, resources were spent on waste disposal and decontamination even though airborne transmission is not affected by these interventions.
- UVGI is not always used effectively. In settings where airborne infection is generated continuously, upper-room UVGI is necessary and requires expertise and good design to be effective.

- An effective respiratory protection program was lacking in most of the institutions of the Russian Federation.
- Engineers and architects lacked the expertise to design, maintain, and commission engineering systems for infection control in hospitals.

Finally, Volchenkov listed opportunities that exist in Russia and could also apply to other BRICS countries:

- The universal availability of electricity allows the use of effective measures, such as upper-room UVGI and ventilation, in high-risk settings.
- Federal and regional funding for infection control has increased substantially in the past 10 years.
- FLD and SLD supply has been sufficient in recent years.
- Rapid molecular methods are becoming available at the regional and district levels, and rapid diagnoses have allowed resources to be devoted to infection control.
- Updated guidelines have improved knowledge of infection control among health care workers and administrators.

At the same time, a lack of knowledge and understanding of several key issues continues to create problems, Volchenkov said. More needs to be learned about the risk of household and community transmission by patients being treated. Questions remain about the criteria for discharge and hospitalization. More evidence also is needed on when isolation can be discontinued for MDR and XDR TB patients in the hospital.

Volchenkov concluded by observing that infection control programs need to have short- and long-term components. They also need to be based on comprehensive risk assessment in the facility, the region, or the country so that policies and regulations are adapted to the situation at hand. Moreover, programs must take health care trends into account, such as the ongoing paradigm shift toward reduced hospitalization and the implementation of new molecular methods. And infection control programs need expert support. Finally, policy makers and politicians should understand that infection control interventions save considerable resources by reducing the incidence of DR TB. Administrative controls can limit the areas, personnel, procedures, and time for which engineering controls and personal respiratory protection are needed. Without effective administrative controls, more expensive environmental interventions are not effective and sustainable.

STOPPING TRANSMISSION IN INSTITUTIONAL AND COMMUNITY SETTINGS[6]

Transmission has become the "elephant in the room" of the MDR TB epidemic, said Edward A. Nardell, Associate Professor, Division of Global Health, Brigham and Women's Hospital, Harvard Medical School. In the past, transmission and reinfection were underestimated, and previously treated patients were said to have acquired drug resistance. But previously treated TB patients can be reinfected, as demonstrated by research results from Russia (Gelmanova et al., 2007), South Africa (Sonnenberg et al., 2001), China (Shen et al., 2006), and other locations. Especially where exposures are common in high-burden areas—including those with high rates of HIV infection—reinfection is to be expected.

Recognition of the importance of transmission and reinfection has a major impact on priorities in TB infection control, on the viability and effectiveness of initiatives focused on latent TB, and on vaccine development. First, known and treated TB patients are not likely to be the major sources of transmission, whether in hospitals or in the community. The greater problem is unsuspected TB patients or unsuspected drug resistance. Nardell cited research from Arzobispo Loayza Hospital in Lima, Peru, where 250 of 349 patients admitted to one female ward in 1997 were screened for TB using sputum, a chest X-ray, a medical history, and a physical exam (Willingham et al., 2001). Forty patients had positive cultures for TB. Two-thirds were smear positive, but 33 percent were unsuspected. Twenty percent had MDR TB, and 6 of the 8 MDR TB patients were unsuspected. Under such circumstances, transmission in a general medical ward is likely, said Nardell.

The configuration and usage of buildings and other aspects of the physical environment are often neglected, but building design matters, said Nardell. Unpublished data, again from Peru, show that the rate of skin test positivity among Peruvian medical students grew from 3.5 percent to 45.9 percent over 7 years. However, the increase was much more substantial for a hospital with a low volume of air space per bed and poor ventilation. The infection rate was much lower in a second hospital with more air space per bed, large windows, and a breezy seaside location.

Since 2008, Harvard Medical School has provided a summer course on building design and engineering approaches for airborne infection control. The course has had a demonstrable effect on the design of facilities to make them less likely to contribute to TB transmission, Nardell said.

Ventilation is another important factor in transmission. Upper-room UVGI can be highly effective and inexpensive compared with other options.

[6] This section is based on the presentation by Edward A. Nardell, Associate Professor, Division of Global Health, Brigham and Women's Hospital, Harvard Medical School.

However, few guidelines exist for its use, and its implementation and maintenance can be poor. In general, air filtration machines and other room air cleaners move too little air to be helpful, said Nardell. UV in ducts and direct UVGI also are not recommended.

Nardell described an experiment in a six-bed ward in which air exposed or not exposed to UV was sent to a set of guinea pigs, animals that are highly susceptible to TB. Treatment with UV light showed about 80 percent efficacy, which was the equivalent of adding approximately 18 air changes to the room. UV treatment requires expertise to design the fixtures and some maintenance, but it can be highly effective.

Nardell concluded by discussing the advantages of avoiding hospitals altogether and relying on community-based treatment. A systematic review of the cost-effectiveness of treatment for MDR TB found that community-based treatment is much less expensive than treatment in hospitals (Fitzpatrick and Floyd, 2012). Experience in Cambodia, Ethiopia, Lesotho, Peru, South Africa, and elsewhere also has demonstrated that such treatment can be highly effective while creating less opportunity for institutional transmission.

Greater likelihood of transmission is a concern with community-based care, but Nardell presented evidence that smear- and culture-positive TB patients on effective therapy do not infect close contacts. Smear and culture positivity correlates with transmission before but not during treatment. In fact, a classic study on infectivity using guinea pigs demonstrated that the effect of treatment on both drug-susceptible and drug-resistant patients was almost immediate (Riley et al., 1959). In contrast, the common rule of thumb that patients need to be treated for 2 weeks before they are no longer infectious appears to have little empirical backing. Patients who infect others are largely those with unsuspected TB or those with DR TB who are on an ineffective therapy, because everyone else is on effective therapy, which stops transmission very quickly. However, effective treatment requires performing rapid and accurate diagnosis and then starting patients on the appropriate therapy quickly.

The situation is somewhat different for XDR TB, whose transmission cannot be stopped with the standard drugs. In these cases—and for TB control in general—Nardell advocates a paradigm known as FAST, for *F*ind TB cases through rapid diagnosis, perform *A*ctive case finding by focusing on cough surveillance, *S*eparate safely and reduce exposure through infection control, and *T*reat effectively based on rapid DST. This approach requires political will and resources, but it can stop transmission in facilities and provides for effective assessment through process indicators and monitoring of cases in health care workers.

8

Rapid Diagnostic Technologies: Status and Limitations

Key Messages[a]

- The rapid detection of drug resistance using molecular diagnostics poses challenges that vary depending on technological and genetic factors.
- Sensitivity and specificity vary by test and patient group and can be critical determinants of whether a diagnostic test is appropriate in a given setting.
- Susceptibility testing of some FLDs and most SLDs can be difficult to standardize, and results often vary across high-quality laboratories.
- Decentralized testing can reduce turnaround time, lower initial default rates, improve communication, and require less reliance on logistics. On the other hand, centralized testing can use sophisticated technology, encompass a broad range of tests, and provide better quality assurance.

[a] Identified by individual speakers.

As emphasized by the speakers on infection control, whose presentations were summarized in the preceding chapter, rapid diagnostic tests are essential to starting MDR TB patients on effective treatment regimens quickly and stopping the spread of the disease. Seven speakers at the workshop examined the state of rapid diagnostic technologies. These tech-

nologies can enable more rapid detection of resistance, but they need to be applied within strong systems that can identify potentially drug-resistant patients, test them quickly, and start them on effective therapies.

GAPS IN DRUG SUSCEPTIBILITY TESTING IN SOUTH AFRICA[1]

The basis for drug resistance in TB is the acquisition of chromosomal mutations, termed *genotypic resistance* by Mark Nicol, Wernher and Beit Professor and Head of the Department of Medical Microbiology, University of Cape Town and National Health Laboratory Service of South Africa. In some cases, those mutations give rise to *phenotypic resistance*—the relative inability of *M.tb.* to grow in the presence of an antibiotic. In turn, phenotypic resistance can be associated with *clinical resistance*, which is a failure of the patient to respond to antibiotic therapy.

Genotypic resistance can be detected by molecular testing using GeneXpert, LPA testing, sequencing, or some other means. Phenotypic resistance is detected by culture-based methods—the failure of the organism to grow in the presence of antibiotic. Clinical resistance to a single drug is usually undetected (because combination therapy is used), but may result in treatment failure or relapse.

Genotypic susceptibility testing is straightforward for some drugs. With rifampicin, for example, almost all resistance is associated with mutations in a very small region, just 81 base pairs, of the *rpoB* gene. Screening that region of the gene can identify rifampicin-resistant strains rapidly and accurately. However, a major problem with genotypic resistance is that the relationship between the genotype and the phenotype may not be clear, especially for some drugs. With some second-line injectable drugs, for example, the drug-resistant population has a higher frequency of certain mutations, but these mutations may also be found in some drug-susceptible strains. A given mutation is not always associated with resistance, whether because of the genetic background of the strain or some other factor. In addition, many of the mutations giving rise to resistance to some drugs remain unknown.

Mutations leading to resistance also demonstrate geographic variability. In Russia, for example, a high proportion of kanamycin resistance is associated with a particular mutation, but that is not the case in South Africa. Thus, a test that works well in South Africa may not work at all or may perform poorly in Russia.

[1]This section is based on the presentation by Mark Nicol, Wernher and Beit Professor and Head of the Department of Medical Microbiology, University of Cape Town and National Health Laboratory Service of South Africa.

People also can be infected with more than one strain of *M.tb*. Whereas phenotypic tests are quite effective in detecting mixed populations of drug-sensitive and drug-resistant bacilli, most genotypic methods are relatively insensitive for this purpose.

Phenotypic tests also pose a variety of problems. They are slow, they rely on culturing the organism, and they can be complex to apply for some drugs. For example, a patient may have low- or high-level resistance, so testing a drug at a single concentration may fail to identify low-level resistance. Furthermore, the resistance levels conferred by different mutations can overlap, thus complicating the identification of a critical concentration for testing at which susceptible strains will not grow but resistant strains will (Böttger, 2011). Biosafety is also a concern when working with large populations of drug-resistant bacilli. Finally, the main problem with clinical resistance is that it is detected only when treatment has failed.

Nicol spoke about LPA testing and GeneXpert testing, which have been implemented sequentially in South Africa as part of large rollout programs. Both techniques have been largely automated, although they still require well-trained personnel. For example, the LPA requires well-designed laboratories and stringent laboratory control to prevent contamination. It has been used successfully in well-run reference or large regional laboratories, said Nicol, but it does not perform as well when the testing is decentralized. "In South Africa one of the mistakes we made was to try to decentralize this assay too far, when in fact it needed to be kept in the centralized facilities for quality-assurance purposes," Nicol said.

The introduction of LPA testing in South Africa had positive although incremental effects on treatment delays, Nicol reported. Data gathered from a low-income housing area on the outskirts of Cape Town showed that its use reduced the median time to treatment initiation for smear-negative patients from 88 to 69 days and for smear-positive patients from 59 to 37 days. The problem in this part of South Africa is that only 30 percent of cases are smear-positive because of high rates of HIV infection, so even with LPA testing, many patients are started on treatment too late. For example, a survey of 73 patients from January 2008 to June 2009 showed that more than half had died while waiting for TB treatment, with a median time of death of 25 days from sputum sampling. "Clearly we needed to do better," said Nicol.

GeneXpert, which uses overlapping DNA probes to detect the presence of mutations, also is highly automated and is relatively easy to use. In evaluation studies, it had high sensitivity and specificity for detection of rifampicin resistance. When it was used for patient management, however, its specificity was somewhat lower because some patients were found to be rifampicin-resistant with GeneXpert but rifampicin-sensitive with the LPA. The problem is that rifampicin-resistant TB is relatively uncommon, which

means that GeneXpert will produce a fairly high proportion of false positives among those cases identified as having rifampicin resistance. Redesign of the test has since improved its specificity.

With GeneXpert, the time between collection of a sputum sample and diagnosis of DR TB was less than 24 hours in demonstration studies in Cape Town. For an LPA performed on a culture sample, the time was around 3 weeks; for an LPA performed directly on a smear-positive sputum sample, it was about 1 week.

In an unpublished study comparing GeneXpert with smear microscopy plus a culture if the smear was negative and a patient was HIV positive, 80 percent of patients with positive GeneXpert results were started on treatment within 1 week. In the routine arm on the study, only about 50 percent of patients were being treated by day 30. However, a high initial default rate, which has been a problem in South Africa, occurred among patients in both arms of the study. Even in the GeneXpert arm, almost 20 percent of patients with a positive test had not been started on TB treatment after 2 months. "You can have the best diagnostic in the world, but unless you have a program that is able to link results . . . to appropriate care, you're wasting your time," said Nicol.

Shortly after the WHO recommendation on diagnostics was promulgated, the minister of health in South Africa made the bold decision to implement GeneXpert testing as a replacement for smear testing. This was a correct and well-informed decision, said Nicol, but the strategy has been complicated by problems with specificity. First, GeneXpert is performed on all patients, not just those suspected of having DR TB. If the GeneXpert results are positive and patients are resistant to rifampicin, they are referred for MDR treatment immediately rather than waiting for confirmatory testing by LPA. This approach again raises the issue of false positives, but Nicol argued that such patients are relatively few in number and can be addressed through other means.

Through the third quarter of 2012, almost 1.5 million GeneXpert cartridges had been procured under concessional pricing, almost half of which came from the South African public sector. At that point in time, the country had more than 100 sites for GeneXpert testing, which had detected about 7,800 rifampicin-resistant cases. The results of this testing have provided an accurate picture of the rifampicin resistance rate in South Africa and, by implication, of the rates of MDR TB. The results also have revealed striking variation among provinces, relative differences that have remained stable since the test was introduced.

The use of GeneXpert in South Africa has reduced to 12 days the gap between collection of the first sputum sample and initiation of treatment for MDR TB. Nicol called this "a tremendous advance" that will make

"an enormous difference in terms of infection-control issues" and lead to a reduction in the transmission of MDR TB.

The GeneXpert-driven algorithm still has several important limitations. It does not include routine isoniazid susceptibility testing, although the significance of this omission is subject to debate. The South African algorithm is complex, especially because it calls for collecting multiple samples from patients. GeneXpert also is more costly than culture-based methods, but it compares favorably with some of the noncommercial phenotypic tests if one considers the infrastructure costs associated with culture-based methods.

The greatest bottleneck currently is the delay in second-line DST. Once patients have been identified as resistant to rifampicin, there is a considerable delay in culture-based susceptibility testing for SLDs. Resistance can be amplified if such patients are given inappropriate or suboptimal MDR TB treatment.

Technologies are being developed to overcome this problem, including microarray systems, phage-based assays, and new phenotypic assays. Nicol focused on three of these new technologies:

1. A second-line LPA targets fluoroquinolones, ethambutol, and injectables. The problem with this test is that its performance varies in different parts of the world depending on the prevalence of resistance mutations. Its sensitivity and specificity also vary for SLDs. Thus, the test can rule in but does not do well at ruling out XDR TB. Also, it can identify a proportion of patients with XDR TB, but that proportion varies geographically.
2. An XDR GeneXpert assay is being developed that targets the same genes as the second-line LPA. However, a decision has not yet been made on whether to continue its development.
3. Various kinds of targeted and whole-genome sequencing can identify specific mutations, can distinguish missense from silent mutations, and may detect mixed allelic variants. However, sequencing requires well-trained staff and costly equipment and poses a bioinformatics challenge when used in routine diagnostics.

A major tension in South Africa is between centralized and decentralized susceptibility testing. There is pressure to decentralize testing, which can reduce turnaround time, lower initial default rates, improve communication, and require less reliance on logistics. On the other hand, centralized testing can use sophisticated technology; allow for a broader range of tests; and provide better quality assurance, which can make it more cost-effective.

DIAGNOSTIC TESTS IN CHINA

Rapid Diagnoses Using the Simultaneous Amplification Test[2]

Jin Chen, Chair, Department of Clinical Laboratory Science; and Deputy Director, Shanghai Key Laboratory of Tuberculosis, Tongji University School of Medicine, Shanghai Pulmonary Disease Hospital, described a new technology used for rapid TB diagnostics known as the simultaneous amplification test (SAT). An isothermal RNA amplification assay for *M.tb*., it has been used in many Chinese TB clinical laboratories with good results. Its target for amplification is the 16S rRNA in the bacterium, which enables the test to perform live bacterial detection. The test has a high sensitivity because one cell has thousands of 16S rRNAs. It has a simple protocol because RNA purification is not required. It also has low cross-contamination, unlike PCR amplification, and can perform rapid amplification under isothermal conditions in just 40 minutes. The total procedure time is about 2 hours once the sputum has been processed, and the results clearly indicate whether a sample is positive or negative.

Based on data collected in his laboratory using 177 sputum samples from TB patients and 67 sputum samples from other lung disease patients, Jin Chen concluded that the SAT is more sensitive and specific than the MGIT 960 mycobacteria testing instrument. For example, the SAT is much better than the MGIT 960 at detecting false negatives.

In a test of rifampicin-sensitive and -resistant and isoniazid-sensitive and -resistant strains, the SAT was clearly able to detect drug resistance. Simple, rapid, cost-effective, and reliable, the technology is suitable for resource-limited laboratories and has already been approved by the State Food and Drug Administration of China.

Using GeneXpert to Detect Drug Resistance[3]

Yao-Ju Tan, Director, Clinical Laboratory Department, Guangzhou Chest Hospital, described an evaluation of the Xpert MTB/RIF test and the effects of gene mutations in DR TB. Xpert MTB/RIF is an automated molecular test for *M.tb*. and resistance to rifampicin that can be performed in less than 2 hours. It uses real-time PCR and requires minimal skill and training, according to Yao-Ju Tan. Its performance has been evaluated in a number of countries, including Azerbaijan, India, Peru, and South Africa.

[2] This subsection is based on the presentation by Jin Chen, Chair, Department of Clinical Laboratory Science; and Deputy Director, Shanghai Key Laboratory of Tuberculosis, Tongji University School of Medicine, Shanghai Pulmonary Disease Hospital.

[3] This subsection is based on the presentation by Yao-Ju Tan, Director, Clinical Laboratory Department, Guangzhou Chest Hospital.

To evaluate its performance in China, sputum samples from 613 patients were analyzed both with the Xpert MTB/RIF test and by conventional DST. The test's sensitivity for detecting rifampicin resistance was 90.9 percent, its specificity was 80.7 percent, and the concordance rate was 86 percent. The positive predictive value was 83.7 percent, and the negative predictive value was 88.8 percent; however, the sensitivity for detecting resistance in smear-negative and culture-positive sputum was only 46.8 percent.

The performance of the test also was evaluated using bronchoalveolar lavage fluid (BLF) from 90 patients. In this case, the test's sensitivity for detecting rifampicin resistance was 90.2 percent, its specificity was 71.9 percent, and the concordance rate was 82 percent. The positive predictive value was 80.4 percent, and the negative predictive value was 85.2 percent. The sensitivity for detecting resistance in smear-negative and culture-positive BLF was higher than with sputum, at 76.5 percent.

The sensitivity for detecting *M.tb.* was 98 percent in smear-positive and culture-positive sputum and 51.6 percent in smear-negative and culture-positive sputum—more sensitive than smear microscopy. The sensitivity was 98.9 percent in smear-negative and culture-negative sputum. Using BLF, the sensitivity for detecting *M.tb.* was 97.6 percent in smear-positive and culture-positive samples and 82.4 percent in smear-negative and culture-positive samples—also more sensitive than smear microscopy. The specificity was 93.8 percent in smear-negative and culture-positive samples.

Yao-Ju Tan also discussed the characteristics of mutations in the *rpoB* gene. Some rifampicin-resistant clinical strains are resistant to rifabutin, which WHO has recommended for the treatment of MDR TB. Sequencing of the *rpoB* gene suggested that these different resistance patterns are due to mutations in different positions or in different combinations in the gene. In particular, the beginning region of the gene may confer both rifampicin and rifabutin resistance, which may make it possible to discriminate rifabutin-sensitive cases and treat them accordingly.

Finally, Yao-Ju Tan spoke about mutations in the *pncA* gene, which encodes an enzyme that activates the anti-TB drug pyrazinamide. Mutations in this gene result in reduced or lost activity of the enzyme and are considered the primary mechanism of pyrazinamide resistance in *M.tb.* Also, mutations in the *rpsA* gene, which encodes a ribosomal protein, can confer increased pyrazinamide resistance. In 120 clinical isolates from the Guangzhou Chest Hospital, the mutations in *pncA* and *rpsA* were detected by DNA sequencing. The greatest number of mutations occurred in *pncA* in pyrazinamide-resistant isolates. However, 29 pyrazinamide-resistant isolates had no mutations in the two genes.

Yao-Ju Tan concluded by noting that the mutation frequency of *pncA* in pyrazinamide-resistant isolates in China is much lower than that seen

in Western countries. This may be the case because most isolates in China have low-level resistance to pyrazinamide.

Use of the LPA in China[4]

Hairong Huang, Deputy Director, National Clinical Laboratory on Tuberculosis, Beijing Chest Hospital, described the use of LPA testing in China. There, two LPA techniques are commonly used: the Hain test from Germany and a domestically produced test called the CapitalBio Microarray. The two tests are similar, both relying on PCR amplification, hybridization, and machine determination of results, although they use different probes.

The Hain test, which is endorsed by WHO for the diagnosis of DR TB, produces similar results in different countries for sensitivity to rifampicin resistance. But its sensitivity for isoniazid resistance varies among countries because the probe covers only some gene mutations.

In 2009, data on the Hain test became available from China, showing that the test's sensitivity is 88 percent for rifampicin resistance but only 80 percent for isoniazid resistance. This finding makes sense, said Huang, because mutations affecting isoniazid resistance in China are different from those in other countries.

Huang also presented unpublished data from four city-level laboratories in four provinces concerning the test's sensitivity for rifampicin resistance as compared with traditional DST. In these cases, the test's sensitivity was relatively low, ranging from 85 percent to 59 percent, although the specificity remained high.

Huang attributed the difference in sensitivities for rifampicin resistance to the difference between research and actual practice. A given test depends not just on technology but also on the skills and performance of the technicians administering it. Even a good technique can produce unimpressive results. These results can complicate the treatment of patients, said Huang. Because the positive predictive values of LPA tests are relatively low, physicians may not know the best way to treat patients. For new cases of MDR TB, for example, the positive predictive value can be as low as 50 percent, which "is really a disaster for a doctor," said Huang. "You cannot make decisions."

Huang urged laboratories to perform traditional DST as well as LPA testing. Doing so means more work for technicians, but is necessary to obtain accurate results until more reliable methods are available. Huang also expressed concern about the long-term sustainability of LPA testing

[4] This subsection is based on the presentation by Hairong Huang, Deputy Director, National Clinical Laboratory on Tuberculosis, Beijing Chest Hospital.

in terms of having the necessary reagents and always being able to cover its costs.

Evaluation of the GenoType MTBDR*plus*[5]

Wei Ge, who presented a talk prepared by Haiying Wang, Shandong Provincial Chest Hospital, described an evaluation of the LPA GenoType MTBDR*plus*. This test was approved by WHO in 2008 for identifying members of the *M.tb*. complex and detecting drug resistance. Using cultivated samples of pulmonary smear-positive patient material, it can identify resistance to rifampicin and isoniazid in about 5 hours.

In the evaluation, 305 stored AFB (acid-fast bacilli)-positive specimens and 118 isolates were submitted to both GenoType MTBDR*plus* testing and traditional DST. For the clinical isolates, the sensitivity and specificity were 100 percent for rifampicin resistance and 88.7 percent and 87.0 percent, respectively, for isoniazid resistance. For the AFB-positive specimens, the sensitivity and specificity for rifampicin resistance were 91.2 percent and 95.4 percent, respectively, and for isoniazid resistance were 85.7 percent and 92.1 percent, respectively.

Ge concluded by noting that the GenoType MTBDR*plus* assay has been validated as a rapid and reliable first-line diagnostic test on isolates or AFB-positive specimens for isoniazid and rifampicin resistance in Shandong. Future work includes rechecking all isolates and specimens for which discordant results were obtained with GenoType MTBDR*plus* and conventional DST.

Use of the GeneChip in China[6]

Pang Yu, Associate Professor, National Tuberculosis Reference Laboratory, National Center for Tuberculosis Control and Prevention, China CDC, described an evaluation of the use of GeneChip for detecting DR TB in China. GeneChip offers a set of analytical platforms that provide rapid, affordable, and substantial information at the DNA or RNA level. GeneChip enables the analysis of thousands of genes simultaneously in a parallel manner across samples. It can be used to scan the gene transcriptional profiles, discover new genes, sequence DNA, and analyze mutations.

The Chinese company CapitalBio developed GeneChip for TB diag-

[5] This subsection is based on the presentation by Wei Ge and Haiying Wang, Shandong Provincial Chest Hospital.

[6] This subsection is based on the presentation by Pang Yu, Associate Professor, National Tuberculosis Reference Laboratory, National Center for Tuberculosis Control and Prevention, China CDC.

nosis. The test is based on detecting the most commonly found mutations in the *rpoB*, *katG*, and *inhA* genes and makes it possible to obtain drug susceptibility results for rifampicin and isoniazid in 8 hours.

Comparison of the results of DST and the GeneChip tests in 330 *M.tb.* isolates and 129 sputum samples produced concordance rates of 91.8 percent for the isolates and 94.6 percent for the sputum samples for rifampicin resistance, said Yu. For isoniazid resistance, the concordance was 70.2 percent for the isolates and 78.1 percent for the sputum samples.

Evaluation of GeneChip for samples from 2,247 smear-positive patients in four cities in different provinces found a sensitivity of 87.6 percent for rifampicin resistance and 80.3 percent for isoniazid resistance, using DST as the gold standard. When GeneChip was used to diagnose MDR TB, the sensitivity was about 73 percent. The positive predictive values for these three outcomes were 84.2 percent, 74.0 percent, and 77.8 percent, respectively.

From these results, Yu concluded that the efficacy of GeneChip is similar to that of imported products, and GeneChip has high acceptability in the hospitals where it is used because of better biosafety. GeneChip can be used for MDR TB diagnosis in China at the city, provincial, and national levels, Yu said.

THE GENETIC DIVERSITY OF DRUG-RESISTANT TB[7]

Many different mutations can lead to the same phenotype of drug resistance, observed Megan B. Murray, Professor, Department of Global Health and Social Medicine, Harvard Medical School. For example, numerous mutations in a number of different genes are associated with isoniazid resistance. In contrast, drug-sensitive TB has very low genetic diversity compared with other bacteria.

Murray and her colleagues have been involved in an effort to develop the TB Drug Resistance Mutation Database, which lists all the mutations found in clinical studies to be associated with resistance and evaluates the strength of the evidence for calling a particular genetic change a drug-resistance mutation. The database contains high-confidence mutations that have been reported repeatedly in large and well-conducted studies, along with a large collection of mutations for which less confidence is warranted because they have not been reported very often or they were reported in lower-quality studies.

Many of the mutations in the database are plausible drug-resistance mutations in that they change molecules in locations that would be expected to affect their function. For example, many mutations that create rifampicin

[7] This section is based on the presentation by Megan B. Murray, Professor, Department of Global Health and Social Medicine, Harvard Medical School.

resistance change the *rpoB* gene in regions that affect the receptor-binding site for rifampicin (although some of the mutations are in locations that appear to be unrelated to the binding site). Similarly, mutations known to cause isoniazid resistance occur in regions involved in the activation and binding of the drug, although mutations occur throughout the molecule involved in activating isoniazid, suggesting that anything that impairs the function of that protein could reduce activation.

With funding from BMGF, the mutation database project launched an initiative to identify mutations and their frequency in drug-resistance genes in *M.tb*. The project developed an archive of 1,800 well-characterized strains from 9 countries and 6 contributing laboratories, sequenced 28 genes and promoters, and created a public database. In addition, a machine-learning approach was used to identify an optimal set of single nucleotide polymorphisms for diagnosing resistance by drug. Selecting a set of mutations that optimizes sensitivity and specificity, this approach identified 24 mutations, all in *rpoB*, that yield a sensitivity of about 93 percent and a specificity of 92 percent. The approach also identified sets of mutations yielding good sensitivity for isoniazid, although the sensitivity was not as good for pyrazinamide and ethionamide, nor was it high for either ciprofloxacin or levofloxacin.

Murray identified four gaps in this analysis, which she labeled the "four Es"—errors, epistasis, efflux, and exotic mutations:

1. Repeated studies comparing the results of DST for FLDs and SLDs across high-quality laboratories rarely produce perfectly concordant results. For pyrazinamide, for example, DST is often inaccurate because the pH of the media can inhibit growth, as can the size of the innocula. But errors can produce a loss of sensitivity in molecular diagnostics, said Murray.
2. Epistasis, or the interaction of multiple mutations, also can be an important factor. On many occasions, and especially with isoniazid, two mutations, each of which causes low-level isoniazid resistance, together cause relatively high isoniazid resistance. If the partner mutation is not detected, identifying a single mutation can lead to an inaccurate result. Furthermore, multiple mutations can produce a stepwise increase in resistance (Meacci et al., 2005).
3. Efflux is a mechanism used by bacteria to extrude toxic substances. Exposing *M.tb*. to one anti-TB drug can cause greater expression of efflux pumps, which can increase resistance to other drugs (Louw et al., 2011). This finding will be explored further in the next few years, Murray said.
4. As an example of exotic or rare mutations, Murray cited rifampicin-resistant isolates that do not have known *rpoB* muta-

tions in the rifampicin resistance-determining regions (Siu et al., 2011); rather, they have mutations in a different part of the gene that affects resistance. These variants are rare, so they do not make a large contribution to overall resistance levels, and they may exact a fitness cost that does not occur with the common mutations. However, some studies have found that rare mutations with fitness costs can subsequently be overcome by compensatory mutations (Pym et al., 2002; Comas et al., 2011).

Genes associated with mutations conferring resistance or a growth or fitness advantage in the presence of a drug are likely to be under strong evolutionary positive selection. To explore this process, Murray and her colleagues sequenced multiple strains of *M.tb*. from around the world, half of which were drug-resistant and half of which were drug-sensitive. Strains that had acquired stepwise resistance to individual drugs over time were oversampled. Using a newly developed technique for detecting selection in the *M.tb*. genome, the researchers identified a set of genes that are involved in the evolution of resistance. Many of these genes have functions that remain unknown, but most with known functions encode cell wall components or are known to be involved in the cell wall's permeability. Some of these mutants may confer low-level resistance, some may be compensatory mutations correcting for a fitness loss from an earlier drug-resistance mutation, and some may be correcting for metabolic changes. "We don't know," said Murray. "It opens up a new avenue for research into drug resistance. It also opens up the idea that what we have considered a very black-and-white, simple process—that organisms acquire drug-resistance mutations and then either are or are not resistant—is a simplification of what actually is going on. There are probably many steps to the acquisition of resistance, and much more to be learned."

9

Addressing Diagnosis and Treatment Across the Spectrum of Drug Resistance

Key Messages[a]

- People who have MDR and XDR TB exhibit a wide variety of patterns of resistance.
- Treatment decisions about these patients often are made in the absence of full susceptibility data, which can result in amplifying resistance.
- Properly applied adjunct therapies can help shorten treatment time, control damage in the lungs, and help establish productive and non-damaging immune responses.
- "Untreatable TB" is a function of both the resistance that exists in the organism and the drugs available to clinicians for the infected patient.
- The term "untreatable" can garner attention among policy makers and the public, but it sends the wrong messages to patients, families, and caregivers.

[a] Identified by individual speakers.

MDR TB is defined as strains of TB that are resistant to at least isoniazid and rifampicin, while XDR TB denotes strains with additional resistance to fluoroquinolones and injectables. TDR TB has been defined as resistance to all available drugs or all drugs tested, although no official definition of the term exists. A session at the workshop focused on issues

of diagnosis and treatment across this broad range of drug resistance, with eight speakers considering both the general topic and treatments directed at specific points along the spectrum of resistance. This session also featured an extended discussion, summarized at the end of this chapter, of the scientific validity and societal implications of using the term "untreatable" TB.

THE SPECTRUM OF MDR AND XDR TB[1]

Patients with MDR and XDR TB exhibit a wide variety of resistance patterns, noted Richard E. Chaisson, Professor of Medicine, Epidemiology, and International Health, Center for TB Research, Johns Hopkins University. To illustrate, Chaisson cited recent data from China (Zhao et al., 2012). According to a national survey conducted by the China CDC, 5.7 percent of new cases and 25.6 percent of retreatment cases had MDR TB. Eleven percent of the new cases and 18 percent of the retreatment cases had what Chaisson called "simple MDR"—resistance to two drugs. At the other end of the spectrum, 8 percent had XDR TB. In the middle, 55 percent of MDR TB patients had ethambutol resistance, and 32 percent had resistance to kanamycin or ofloxacin.

Similarly, in a study of more than 1,200 patients with MDR TB from eight countries, half had resistance to all FLDs tested, and a large proportion had resistance to SLDs as well (Dalton et al., 2012). More than 40 percent had resistance to at least one SLD, 20 percent to an injectable, and 13 percent to a fluoroquinolone, and 6.7 percent had XDR TB. Thus, resistance is highly heterogeneous in this sample, and studies of other populations have found similar variety (Salvo et al., 2012).

Clinicians frequently know nothing about this heterogeneity when they make treatment decisions. As pointed out earlier in the workshop, new technologies for detecting and characterizing MDR TB work very quickly. In real life, however, other problems can delay the results of drug susceptibility tests. In laboratories studied in South Africa, for example, the availability of Hain genotyping reduced the period from sputum collection to availability of drug susceptibility results in half, but 26 days still separated the two (Hanrahan et al., 2012). Furthermore, the median time to the initiation of treatment remained 62 days because of the challenges of implementing the test in a clinical setting.

There is a large menu of drugs for the treatment of MDR TB, Chaisson pointed out (Table 9-1), some newly developed and others older and with unclear efficacy. But patients can be treated only with those drugs that are available in the settings where they are being treated. If a preferred drug

[1] This section is based on the presentation by Richard E. Chaisson, Professor of Medicine, Epidemiology, and International Health, Center for TB Research, Johns Hopkins University.

TABLE 9-1 Drugs Used to Treat MDR TB

Group	Drugs
Group 1: First-Line Oral Drugs	Ethambutol (E) Pyrazinamide (Z) High dose INH (H)
Group 2: Injectable Drugs	Kanamycin (Km) Amikacin (Am) Capreomycin (Cm)
Group 3: Fluoroquinolones	Moxifloxacin (Mfx) Levofloxacin (Lev) Ofloxacin (Ofx)
Group 4: Oral Bacteriostatic Second-Line Drugs	Ethionamide (Eto) Prothionamide (Pro) Cycloserine (Cs) OR Terizidone (Trd) Para-aminosalicylic acid (PAS)
Group 5: Drugs of Unclear Efficacy	Clofazimine (Clo) Clarithromycin (Cla) Amoxacillin-clavulanate (Aug) Linezolid (Lz) Thiocetazone (T)
Group 6: New Products (approved or via compassionate use)	Bedaquiline Delaminid PA824

SOURCE: Chaisson, 2013. Presentation at the IOM workshop on the Global Crisis of Drug-Resistant Tuberculosis and the Leadership of the BRICS Countries: Challenges and Opportunities.

is not available, patients are treated with the drugs at hand, which can amplify resistance.

Drugs may not be available for many reasons. Manufacturing problems may force factories offline. Regulatory barriers may block drugs that are being manufactured, have yet to be manufactured, or have yet to be approved. Forces in the marketplace also can affect the availability of products. Supply-chain management can pose major problems (see Chapter 10), as can cost. In India, for example, linezolid would be extremely useful, but it is unaffordable, said Chaisson. Similarly, during the past 2 years, India has experienced shortages of imipenem, linezolid, moxifloxacin, and rifampicin. Uganda has seen shortages of all FLDs because of management problems. Even in the United States, shortages of amikacin, capreomycin, clofazimine,

cycloserine, ethambutol, kanamycin, and PAS have occurred in the past year. And isoniazid is in short supply worldwide because of the Fukushima earthquake and tsunami, which destroyed the plant that manufactured the bulk of the material used to produce the world's supply of that drug.

"Untreatable TB" is a function of both the resistance that exists in the organism and the drugs available to clinicians for treating the infected patient, Chaisson concluded. As described in the final section of this chapter, many problems surround the use of this term.

THE NEED FOR A PARADIGM SHIFT IN THE TREATMENT OF THE SPECTRUM OF DRUG-RESISTANT TB[2]

Adjunct treatment protocols are part of what Markus Maeurer, Professor and Head, Division Therapeutic Immunology, Department of Laboratory Medicine and Department of Microbiology, Tumor, and Cell Biology, Karolinska Institutet, called the "entire picture" of TB treatment. A patient with sepsis is treated not just with antibiotics but also with individually tailored therapy, which may include anti-inflammatory treatments, to address the clinical situation. However, this does not happen with MDR TB.

Maeurer reflected on what can be done to treat chronic inflammation and presented preliminary results of a small Phase I clinical trial conducted with colleagues in Belarus. First, patients with MDR TB tend to produce more gamma-interferon than those with drug-sensitive TB, although this is not true for gamma-interferon responses to cytomegalovirus or Epstein-Barr virus. Also, the lung tissue of patients with MDR TB is being destroyed through fibrosis of the alveoli and bronchioles even when the *M.tb*. infection is controlled. Lung immune responses are poor or nonexistent, causing major problems with oxygenation. This process is driven by TGF-beta production, with greatly increased collagen synthesis.

One way to treat this problem may be to address long-term inflammatory processes and provide access to drugs, particularly given the overproduction of collagen in MDR TB patients, Maeurer said. Enhancing the immune response at the wrong time and in the wrong place can harm a patient. But properly applied adjunct therapies can help shorten treatment time, control damage in the lungs, and help establish productive and nondamaging immune responses.

With sepsis, initial interferon delivery may endanger the patient, but interferon in the "contraction" phase of the immune response leads to significantly increased survival, counteracting interleukin 10 and TGF-

[2] This section is based on the presentation by Markus Maeurer, Professor and Head, Division Therapeutic Immunology, Department of Laboratory Medicine and Department of Microbiology, Tumor, and Cell Biology, Karolinska Institutet.

beta. Similarly, in influenza infection, death can result from the "cytokine storm" designed to protect from infection. Therefore, some influenza patients are treated with cyclophosphamide, which controls the immune response (Henter et al., 2010). Adjunct therapies also are being used successfully in cancer treatments.

More evidence on the effects of adjunct therapies in TB is available than many realize, said Maeurer. Children with TBM are conventionally treated with glucosteroids. However, host-derived therapies that address excess inflammation are associated with better survival in these patients (Tobin et al., 2012). Likewise, studies have shown that both glucocorticosteroid treatment (Muthuswamy et al., 1995) and anti-tumor necrosis factor treatment (Wallis, 2005) may accelerate *M.tb*. clearance in patients with pulmonary TB. In general, said Maeurer, key pathways in inflammation, tissue damage, and subsequent loss of immune control are as yet untapped.

Robust markers are needed for adjunct therapies if they are to be incorporated into clinical protocols. Experience shows that the state and extent of inflammation are critical. But many existing drugs target biologically and clinically relevant pathways. For example, some antimalaria drugs affect major histocompatibility complex (MHC) expression on macrophages. "Do not be afraid of cellular therapy," Maeurer urged.

Finally, Maeurer shared some results from a Phase I clinical trial conducted with colleagues in Belarus, where the number of MDR/XDR TB patients constitutes a crisis. The trial used stromal cells harvested from the bone marrow aspirate of XDR TB patients. The cells were grown for 2–3 weeks and reinjected initially into 9 and subsequently into 20 more patients. Six of the initial 9 patients responded well, as did a similar percentage of the next 20 patients. Patients regained immune responses, as indicated by gamma-interferon production directed against TB antigens. In patients who responded, the treatment reduced unproductive inflammation, rebuilt lung tissue, and refocused the anti-TB immune response. "It's not dangerous," said Maeurer, "and there may be beneficial effects, which is not so surprising, because you're dampening the immune system in a productive way."

Maeurer concluded by calling for more scientifically and clinically relevant models and Phase I trials involving experts not just in TB but also in other diseases, including cancer. "We are not alone," Maeurer said. "This is done in other fields, and it works perfectly well." In particular, he noted in responding to a question from the audience, many drugs used in Chinese medicine have effects on inflammation.

MDR, XDR, AND UNTREATABLE TB IN AFRICA[3]

Martie van der Walt, Interim Director, Tuberculosis Epidemiology and Intervention Research Unit, South African Medical Research Council; and Professor, Department of Internal Medicines, Faculty of Health Sciences, University of Pretoria, South Africa, highlighted the challenges of DR TB, including what has been termed "untreatable" TB, in the African context. The world has made great progress in reducing TB incidence, prevalence, and mortality, she said. However, progress in responding to DR TB remains low. During 2011, in the 27 HBCs, 60,000 MDR TB patients were diagnosed, and this number is a large underestimation, van der Walt said. Furthermore, the average rate of XDR TB among these patients is 9 percent.

Although Africa has a small percentage of the world's population, it has a high burden of both TB and DR TB, along with high HIV infection rates. According to WHO (2012), the success rate for MDR TB treatment for Africa in general is only about 45 percent, and the death rate is higher than in any other WHO region. The default rate also is relatively high, which is a concern because defaulted or intermittent therapy drives drug resistance.

Of the 43 African countries covered in the WHO report, only 10 have culture capability, and only for FLDs. This limitation contributes to a marked lack of data for many African countries. Also, many countries do not treat TB with kanamycin and ofloxacin and therefore do not test for XDR TB.

Only two laboratories in Africa, both in South Africa, perform second-line DST. Some other countries in the region can perform first-line DST, but they do not do so universally because the cost of both the testing and the drugs is prohibitive. In addition, clinicians have limited experience treating patients with SLDs, and many are concerned about overlapping toxicity with HIV drugs.

The two laboratories in South Africa that perform second-line DST—the National Health Laboratory Service and van der Walt's institution—are in Gauteng province in the north. Although the highest burden of TB is in the Eastern Cape and KwaZulu-Natal provinces, South Africa is fortunate to have a good specimen transportation system, such that specimens from even the most remote parts of the country can be delivered to one of these laboratories for DST within 3 days.

One reason for the low coverage of DST in African countries is uncertainty about when and whom to test. For example, when should a sample be collected for second-line DST? Should universal screening be conducted

[3] This section is based on the presentation by Martie van der Walt, Interim Director, Tuberculosis Epidemiology and Intervention Research Unit, South African Medical Research Council; and Professor, Department of Internal Medicines, Faculty of Health Sciences, University of Pretoria, South Africa.

at case finding, at treatment initiation, or at regular intervals thereafter? Should attention be focused on particular populations, such as those who default, relapse, or do not culture convert? Should health care workers or other high-risk populations be tested? Should all patients with any rifampicin resistance undergo full DST? "I personally think this is the way to go," said van der Walt. "The technology isn't there, but we need to have a point-of-care microarray test that will give us, within a couple of minutes, results. Of course, then we also need the drugs."

In addition, organizing and running a laboratory network is expensive and requires trained staff. DST needs to be performed in a biosafety level 3 facility, which further raises costs. Even transportation of infectious material is an issue, because it requires accredited couriers. DST is slow and cumbersome, and contamination is a problem.

Today, second-line DST is a culture-based method that takes 12 weeks, or probably longer, to confirm that a patient with suspected MDR TB has additional resistance. Should empirical treatment be started, or should the initiation of additional treatment be postponed? If treatment is postponed, should the patients be kept in the hospital or sent home?

South Africa has an algorithm for the early detection of MDR TB that involves microscopy laboratories, the use of LPAs, and culture laboratories. Throughout this process, specimens need to be traced so patients need not be recalled to obtain new ones.

Van der Walt also emphasized the quality control issue with second-line DST. Unless the quality of the diagnosis is high, defining such concepts as "untreatable TB" will be difficult. One mechanism for ensuring quality control is the WHO's Supranational Reference Laboratory Network, created in 1994 to support the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. The objectives of the Global Project are to estimate the magnitude of drug resistance globally, determine trends, and provide data to inform WHO policy decisions. The Supranational Reference Laboratory Network monitors the proficiency of National Reference Laboratories in susceptibility testing of anti-TB drugs, thereby ensuring quality-assured diagnoses of drug resistance. In South Africa, van der Walt's laboratory provides these services for many of the countries of sub-Saharan Africa as well as for the South African TB control program.

Finally, van der Walt emphasized the importance of testing for drug resistance even in countries that do not treat XDR TB patients because they cannot afford the drugs. Migratory workers from many countries in Africa work in South Africa's mines, and rates of TB among these mineworkers are some of the highest measured in the world—an estimated 3,000 to 7,000 per 100,000. Risk factors include the silica dust generated in the mines, reinfection caused by poor infection control and ongoing transmission, and high levels of HIV infection. When mineworkers contract DR TB in South

Africa, they can take the disease back to their home countries, making it important for them to be tested to reduce the spread of the disease.

Some thoughts on "untreatable" TB concluded van der Walt's presentation. MDR and XDR TB are manmade problems, she said, exacerbated by high default rates, nonadherence, drug toxicity, and inappropriate use, and untreatable TB is following the same course. The reliability of DST will be critical to the design of individualized regimens for these patients. In addition, more needs to be learned about the connections among clinical failure, phenotypic resistance, and detection of mutations. Enhanced drug resistance also will require standardization of tests and expanded laboratory capacity. Finally, the idea of untreatable TB raises ethical issues involving health care and human rights.

MDR, XDR, AND UNTREATABLE TB FROM A LABORATORY PERSPECTIVE[4]

Failure to treat MDR and XDR TB patients correctly will create problems in the future, including the possibility of untreatable TB, said Sven Hoffner, Director, WHO Supranational Tuberculosis Reference Laboratory; and Department for Preparedness, Swedish Institute for Communicable Disease Control. He defined TDR TB as infection with a strain of TB that is resistant to all of the drugs available at a given time or place, as well as being more resistant than XDR TB. He then defined untreatable TB as a case of TB so severely drug resistant that a patient cannot be cured with any existing drug therapy. He acknowledged, however, that no official definitions of these terms exist. They are useful for advocacy and fundraising purposes, but the signals they send to individual patients and health care workers need to be considered.

Nevertheless, such strains do exist and are being transmitted, said Hoffner. They constitute an increasing public health threat and require modifying international guidelines accordingly. They also must be detected promptly if efforts to limit or stop the development of further resistance and the transmission of such strains are to be maximized.

XDR TB cases have been detected in many countries, Hoffner said, and those countries that have not detected such cases generally lack the laboratory capacity to do so. In sub-Saharan Africa and South Asia, too few culture laboratories exist to meet the demand. Furthermore, creating laboratories that meet WHO's biosafety standards is difficult, expensive, and time-intensive. "I doubt that this is the way forward," Hoffner said. Even in

[4] This section is based on the presentation by Sven Hoffner, Director, WHO Supranational Tuberculosis Reference Laboratory; and Department for Preparedness, Swedish Institute for Communicable Disease Control.

Europe, the proportion of laboratory-confirmed TB cases is low, so patients are treated without knowledge of whether they are drug resistant. Outside of Europe and the Americas, DST of both new and re-treated TB patients for rifampicin and isoniazid is well below 10 percent, and testing for SLD susceptibility occurs worldwide for only about 20 percent of MDR TB patients. "Perhaps we need to rethink what we are doing," Hoffner said.

Hoffner discussed results on drug resistance from Belarus and Iran. In Belarus, surveillance for drug resistance performed in Minsk in 2010 and 2011 found the highest-ever reported figures from a quality-assured study (Skrahina et al., 2012). Among new TB cases, 29.2 percent and 35.3 percent, respectively, had MDR TB in the 2010 and 2011 surveys. Among previously treated cases in the 2011 survey, 76.5 percent had MDR TB and 19.4 percent XDR TB. Overall, 49 percent of the infectious cases of TB in Minsk city were MDR TB, and Hoffner cited unpublished data indicating similar levels in other regions. Furthermore, the clustering of cases points to ongoing transmission and the need for infection control. This information "must lead to some rethinking of how we are controlling the problem and what is needed also from the laboratory side," Hoffner said.

In Iran, based on specimens collected over 2 years in the national reference center in Tehran, 5.4 percent of 146 MDR TB isolates proved to be XDR TB, and 10.2 percent were TDR TB, which Hoffner defined as resistance to all 13 of the drugs tested—amikacin, capreomycin, ciprofloxacin, cycloserine, ethambutol, ethionamide, isoniazid, kanamycin, ofloxacin, PAS, pyrazinamide, rifampicin, and streptomycin (Velayati et al., 2009). Among the latter 15 patients, 11 were men, and 7 were immigrants from the neighboring countries of Afghanistan and Azerbaijan. These patients all had different genotypic profiles, although primary MDR TB patients were not included in this group, which may have suggested transmission.

Hoffner emphasized the importance of rapid detection of resistance to rifampicin and isoniazid for timely modification of drug regimens so that MDR TB patients can quickly become noninfectious and then cured. He also stressed the need for an early warning system for MDR TB. Prompt identification of patients with drug-resistant strains would enable more rapid initiation of treatment, better infection control measures, and thus reduced development and spread of MDR TB.

In response to the observation that rapid testing is costly, Hoffner pointed out that, given the cost of the additional TB cases such testing can avoid, it is in fact extremely cost-effective. Furthermore, the cost of rapid testing is small compared with that of other kinds of tests.

Hoffner concluded with a list of priorities for TB laboratory services:

- A new algorithm is needed that takes new diagnostic possibilities into account. The roles of microscopy, culture, drug susceptibility

tests, and rapid molecular tests should be optimized to allow sensitive, specific, and timely detection of MDR and XDR TB.
- Necessary resources should be made available for implementing more rapid tests as soon and as widely as possible.
- Unnecessary routine examinations should be discontinued to lower overall costs and make financial and physical space for improved techniques.
- A plan for the future organization of national laboratory networks should be formulated that accounts for the implementation of new techniques.
- A set of basic quality criteria and a licensing system should be established to ensure high-quality service. Standard operating procedures should be developed and implemented, and laboratories failing to meet quality standards should be offered training and if necessary closed.
- Methods for determining susceptibility to new drugs should be developed. These methods could include both phenotypic and genotypic testing.
- A human resources development plan should be established both to replace people leaving and to guarantee relevant knowledge in new techniques.
- Infection control in TB laboratories needs to be improved, in part through a risk assessment of all diagnostic units and of the tests carried out.
- Training needs should be analyzed and gaps filled.
- Operational research should be strengthened.

Complementing Hoffner's presentation were remarks by two speakers from China who discussed the diagnosis and treatment of two different forms of TB—TBM and endobronchial TB. These presentations are summarized in Boxes 9-1 and 9-2, respectively.

BOX 9-1
A New Approach to Diagnosis of TBM[a]

TBM, an extrapulmonary disease in the central nervous system caused by *M.tb.*, is associated with high mortality rates (up to 30 percent). Infection may lead to brain damage that causes abnormal behav-

continued

BOX 9-1 Continued

ior, mental impairment, motor paralysis, and seizures. As pointed out by Xiaoyou Chen, Director and Chief Physician, Tuberculosis Department, Beijing Chest Hospital, Beijing Tuberculosis and Thoracic Tumor Research Institute, rapid diagnosis and early intervention are vital if patients are to have successful outcomes.

The exact global incidence and prevalence of TBM are unknown. Data from 2010 indicate that 5.5 percent of extrapulmonary TB cases—equivalent to 1.2 percent of total TB cases—involve central nervous system TB (Takahashi et al., 2012). In Beijing Chest Hospital, the number of TBM cases rose from about 30 in 2001 to about 150 in 2012, according to Xiaoyou Chen.

Approximately 90 percent of patients are diagnosed in stage II or III, which means they are diagnosed late. Clinical response to anti-TB therapy in all forms of TB in the central nervous system is excellent if the diagnosis is made early, before irreversible neurological deficit is established. Early diagnosis of TBM is therefore considered a key to effective treatment and a good prognosis.

Diagnosis of TBM remains a major challenge because of inadequate diagnostic methods and the poor sensitivity and specificity of existing markers. Diagnosis is based on the clinical picture, neuroimaging abnormalities, changes in cerebrospinal fluid, and the response to anti-TB drugs. But the clinical manifestation—including fever, headache, and vomiting—is broad and not specific to TBM patients, so early diagnosis is difficult.

Bacteriological culture from cerebrospinal fluid is the gold standard for the diagnosis of TBM but is expensive, requires significant laboratory infrastructure and expertise, and takes too long to guide patient management efficiently (Torok et al., 2008). In Xiaoyou Chen's practice, no more than 10 percent of TBM patients are culture positive from cerebrospoinal fluid.

Mass spectrometry-based quantitative proteomics has emerged as a powerful means of identifying and studying disease biomarkers that serve as indicators of disease progression, prognosis, and drug safety and can help elucidate the mechanism of drug treatment. In a recent study, Xiaoyou Chen and his colleagues used a quantitative proteomic approach to identify 338 differentially expressed peptides/proteins from the cerebrospinal fluid of TBM cases as compared with controls (non-meningitis patients). They are now engaged in further work to confirm which of these markers will be useful for the diagnosis of TBM.

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[a] This box is based on the presentation by Xiaoyou Chen, Director and Chief Physician, Tuberculosis Department, Beijing Chest Hospital, Beijing Tuberculosis and Thoracic Tumor Research Institute.

BOX 9-2
Surgical Treatment of Endobronchial TB[a]

Endobronchial TB is defined as a TB infection of the tracheobronchial tree with microbial and histopathological evidence. The clinical manifestations may be acute, insidious, or delayed and include cough, expectoration, hemoptysis, shortage of breath, wheezing, and fever. Ten to 20 percent of patients may have a normal chest radiograph.

The goals of therapy, said Xiao Ning, Thoracic Department, Beijing Chest Hospital, Beijing Tuberculosis and Thoracic Tumor Research Institute, are to eradicate *M.tb.* and to prevent tracheobronchial stenosis, although the course and prognosis of the disease vary widely. In the active stages of disease, anti-TB chemotherapy is generally a combination regimen comprising 4 kinds of anti-TB drugs, with treatment usually lasting more than 9 months. Localized treatments include inhalation of nebulized anti-TB drugs and lavage or submucous injection of the diseased region with anti-TB drugs.

For patients in whom fibrostenosis has already developed or extensive granulation tissue appears, anti-TB chemotherapy is of limited efficacy. Surgical removal using a bronchoscope can be used to treat tracheobronchial stenosis shaped by extensive granulation tissue. Available approaches include laser ablation, microwave ablation, electrocautery, and cryotherapy. Fibrostenosis also can be treated with balloon dilation and stent implantation. Severe tracheobronchial stenosis that cannot be relieved by medical treatment may require chest surgery.

Most patients have a good prognosis, with the most frequent complication being anastomotic stenosis. Lobectomy or pneumonectomy with trachial or bronchial plasty is a useful technique in the latter cases.

[a] This box is based on the presentation by Xiao Ning, Thoracic Department, Beijing Chest Hospital, Beijing Tuberculosis and Thoracic Tumor Research Institute.

TOTALLY DRUG-RESISTANT TB IN INDIA: LESSONS AND OPPORTUNITIES FROM A CLINICAL PERSPECTIVE[5]

TB exists on an epic scale in India. The country sees fully 3 million cases of active TB and 300,000 fatalities every year (WHO, 2012).

Zarir F. Udwadia, Consultant Chest Physician, Medical Research Council, Hinduja Hospital and Research Centre, Mumbai, personalized

[5] This section is based on the presentation by Zarir F. Udwadia, Consultant Chest Physician, Medical Research Council, Hinduja Hospital and Research Centre, Mumbai.

the epidemic by recounting the history of a 37-year-old female who lived in India's largest slum, Dharavi, Mumbai. She had a history of pulmonary TB for 5 years; had seen multiple physicians; and had taken almost every available FLD and SLD, often in incorrect doses and with considerable toxicity. However, she had never undergone DST. She came to Udwadia after hearing about enrollment for an NIH-funded study of XDR TB.

When this patient was tested for drug susceptibility, she proved to be resistant to 11 drugs—amikacin, capreomycin, ethambutol, ethionamide, isoniazid, kanamycin, moxifloxacin, ofloxacin, PAS, rifampicin, and streptomycin. A salvage regime that included isoniazid, capreomycin, linezolid, clofazine, and cycloserine was initiated. After 2 months of treatment, the patient underwent a right-sided pneumonectomy. She was doing well enough on the first day after the operation, but then went into a rapid decline and died on the fourth day from refractory hypoxemia.

Udwadia listed the lessons he learned from this patient:

- Untreatable forms of TB are increasingly being encountered.
- Such patients have virtually no drug options.
- New drugs are desperately needed.
- The cost of DST is money well spent and is a fraction of the overall cost of treatment.
- Surgery is often the sole option for such patients.
- In no other disease is prevention more important than in TB.

In the next few weeks, Udwadia saw three more cases from different parts of Mumbai with the same drug-resistance pattern, all in the free weekly clinic he has been running at Hinduja Hospital for the past two decades (where, he said, "I have witnessed firsthand the horrendous amplification of resistance over the decades"). The hospital is a large private facility with an advanced mycobacterial laboratory that essentially acts as the reference laboratory for the city. A publication on these and other cases, entitled "Emergence of New Forms of Totally Drug-Resistant Tuberculosis Bacilli" (Udwadia et al., 2012), caught the attention of the *Times of India*, leading to a media flurry. The government seized the cultures from the hospital laboratory, and the authors were pressured to retract the paper.

WHO's responses were more measured, said Udwadia. Within a few weeks of the article's publication, WHO's website included frequently asked questions about TDR TB, and WHO held a meeting 2 months later in Geneva to discuss nomenclature. WHO's Paul Nunn described the cases as "a wake-up call for countries to accelerate provision of proper care to MDR patients."

Participants in the March 2012 meeting in Geneva concluded that reports of TB patients with patterns worse than XDR are increasing and

present a formidable challenge. However, participants did not recommend a new definition of resistance beyond XDR TB because most laboratories already struggle to diagnose MDR TB, and the new designation would further stress their capacity. The meeting also called attention to concerns about the reliability, reproducibility, accuracy, and in vivo correlation of susceptibility testing for SLDs.

In May 2012, the supranational reference laboratory to which the samples had been sent verified that the strains "are indeed resistant to all 12 drugs as reported" by the article. The article's publication was responsible at least in part for a number of important changes:

- Free drugs were offered to all the surviving patients, six of whom accepted.
- Cluster investigations of their 43 contacts were initiated.
- Notification of MDR TB was made compulsory in Mumbai, which resulted in a doubling of MDR TB notifications in 6 weeks compared with the previous 18 months.
- The capacity of two state laboratories designated for closure was strengthened.
- Staffing and funding for TB control were increased.
- The health secretary wrote to each state directing the scale-up of DOTS-Plus.
- The FDA commissioner spoke about reregulating the use of TB drugs.

In January 2013, Hinduja Hospital and Research Centre received the "TB Champion of 2013" award from The Union.

Since the article's publication, 16 more cases of TDR TB have emerged. According to Udwadia, "they hold a mirror to the way that this disease has been mismanaged in India over the decades." Cases have occurred among young people, male and female alike. These patients have seen an average of four doctors and received a mean of 10 drugs over an average of 26 months before receiving a diagnosis of TDR TB.

The diagnosis of "untreatable" continues to generate controversy (Cegielski et al., 2012). As described in the final section of this chapter, some object to calling a disease untreatable if any treatments are possible. In that regard, Udwadia quoted Plato: "I have no objection to your giving names any significance you please if you will only tell me what you mean by them." (As Paul E. Farmer, Partners In Health, Harvard Medical School, and Brigham and Women's Hospital, said in his opening remarks at the workshop, even MDR TB is "just a definition.") Some forms of DR TB have a worse prognosis and outcomes based on the number of drugs to which a patient is resistant. Udwadia also said that each initial before

"DR" is "a reflection of our failure." Meanwhile, "TDR TB" is being used by patients and is a familiar term online, with more than a million hits on Google. The term is not just a matter of semantics, said Udwadia. It means something to patients about their treatment and survival.

TB patients in India face a Faustian choice, Udwadia said. Thirty percent go to the public system, which offers little choice of treatment and can have the effect of amplifying resistance. The other 70 percent go to the private health care system, but many see nonspecialists, including providers who offer low-quality alternatives to conventional care. "A tiny fraction of the MDR patients are going to end up cured," said Udwadia.

Udwadia characterized the dilemma of MDR and XDR TB in India, which he described as public health *realpolitik*:

- The country has a large and expanding population.
- MDR and XDR TB patients are accorded the status of untreatable and untouchable.
- The national TB program has turned a blind eye to them.
- WHO focuses on DOTS, which has been a tremendous public health success for the country but only for drug-sensitive patients.
- Treatment of MDR TB is not considered cost-effective, because many drug-sensitive patients can be cured for the cost of treating a single patient with MDR TB.

Udwadia quoted Farmer: "Our mission must be to treat the sick, not just the sick who can pay. Our mission must be to treat TB regardless of resistance pattern. . . . It is failure to treat, not treatment failure, that accounts for the vast majority of MDR TB deaths."

After a year of individualized regimens for each of the 20 TDR TB patients Udwadia has seen, 6 have died, and 3 have been lost to follow-up. But seven have shown radiological improvement, five have culture-converted, seven have smear-converted, and seven have shown clinical improvement. "So, TDR does not mean totally doomed, which is again something the press seized on," said Udwadia.

Udwadia listed several difficult questions that surround these patients:

- How do we treat XDR TB patients who have failed treatment?
- What do we do when we have run out of all drugs, and surgery is not possible?
- Do we continue to treat with the aim of reducing infectiousness rather than curing?
- Should we have a protocol for withdrawal of all drugs as we do in cancer patients?
- What emotional support do we give these patients?

Finally, Udwadia offered some suggestions based on his experiences:

- Laboratory capacity needs to increase. India has one supranational reference laboratory, yet the country bears a large burden of MDR TB. Fewer than 1 percent of MDR TB patients in the country receive DST.
- All patients who fail to respond to DOTS need to receive DST early on rather than being subjected to 8 months of demanding treatment.
- GeneXpert needs to be rolled out across the country. "South Africa is an inspiration in that regard," said Udwadia.
- DOTS-Plus needs to be expanded countrywide.
- Additional funds are needed. Funds should not be diverted from drug-sensitive patients to cure MDR TB patients. That would be inappropriate.
- New drugs are needed, and until they are available, existing drugs should not be squandered. The development of new drugs will require that pharmaceutical companies work together.
- Not just new drugs but new regimens of existing or novel drugs are needed.
- The dysfunctional relationship between the private and public health care sectors needs to be improved through public–private partnerships.
- Legislation is needed to ensure that only designated specialists can treat MDR TB.

Udwadia concluded by quoting Yale lecturer Jonathan Smith: "It's not that we can't cure TB, it's that we can't cure TB for poor people. TDR TB has been present for decades, but instead of pathological resistance the culprits are apathetic governments, broken promises, and non-functioning infrastructures that elude accountability. . . . TDR TB reinforces my claim that TB management should be deemed the largest violation of human rights the global health community has ever seen"—a sentiment with which Udwadia heartily agreed.

TB TERMINOLOGY AND ADVOCACY NEEDS

Following the presentations on diagnosing and treating across the spectrum of drug resistance, an extended discussion took place regarding the use of the term "untreatable" TB. Chaisson began by pointing out that people with untreatable TB are not really untreatable. The patients with so-called TDR TB in India were and continue to be treated. As new drugs are developed, moreover, new treatments will become available, as has

occurred with HIV infection. Thus, using the term "untreatable" sends the wrong message, Chaisson said. A term should not convey that a patient is doomed. Rather, drug resistance occurs along a spectrum from none to a great deal, and recognizing the existence of that spectrum is more important than calling a particular point on the spectrum untreatable.

Farmer also took issue with the term "untreatable." Before streptomycin was introduced, an effective set of interventions for TB did not exist. As antibiotics were developed, TB changed from an untreatable to a treatable disease. Similarly, leukemia in children used to be almost 100 percent fatal, but new treatments have resulted in good survival rates. Thus if new treatments can be developed and integrated into enabling platforms, untreatable diseases can become treatable. In fact, Farmer prefers the term "drug-resistant" TB to "MDR TB" so as not to dwell on the exact definition of MDR TB, XDR TB, or other forms of resistance. The term "untreatable" is not accurate clinically, sociologically, or historically, said Farmer. Families will always try to get treatment for sick members, and professionals will seek to treat them. The important thing is to ensure that treatments are effective and do not risk amplifying resistance.

Neel R. Gandhi, Rollins School of Public Health, Emory University, pointed to the value of a term that would acknowledge the diversity of resistance beyond MDR and XDR TB. Patients who are resistant to 12 or 15 drugs are much more difficult to cure than those who are resistant to just 2 or 3 drugs. Anne E. Goldfeld, Harvard Medical School and GHC, emphasized the need to call attention to the problems entailed in procuring the drugs that can cure people on the far end of the resistance spectrum. In that respect, the situation with TB is different from that with forms of cancer that are untreatable. "Why don't we have in our hands the ability to treat our fellow humans with what is available?" asked Goldfeld.

Gail Cassell, Harvard Medical School and Infectious Disease Research Institute, said she is sympathetic to the argument that in reality, TB occurs on a spectrum, and the term "untreatable" may not always be clinically accurate. But she also spends a great deal of time trying to generate funding for the treatment of DR TB, and the TB advocacy community needs powerful terminology to convey the urgency of the situation to the public and policy makers. Cassell suggested that discussion of the spectrum of resistance does not adequately communicate the severity of the problem. "If we hadn't come up with the term MDR, I don't think we would be treating nearly as many patients as we are today," she said.

Participants discussed several possible terms as alternatives to untreatable, such as SXDR (for super XDR), XXDR (for extremely drug resistant), or CXDR (for completely drug resistant). Another possibility suggested was to assign resistance a number corresponding to the number of drugs to which a patient is resistant—thus, for example, 6DR, 10DR, or 15DR.

Rifat Atun, Imperial College London, argued that a new term is unlikely to capture the attention of the policy makers who determine how much funding will be available for TB treatment. What will inspire them to action, he said, is the message that DR TB is a security risk that can affect any nation.

Edward A. Nardell, Brigham and Women's Hospital, Harvard Medical School, observed that even today some drugs are available that are not being used to treat TB but may have an effect on the disease, even if they are not strong drugs. An alternative delivery system, such as the airway, may be needed for these drugs, but their existence and potential to treat DR TB demonstrates further that the disease is not untreatable.

Chaisson questioned whether intensifying the rhetoric surrounding DR TB will be effective. In HIV advocacy, this tactic has not been the solution to the problem. Rather, advocates have emphasized that millions of people are dying and that it is unacceptable not to treat them. In response, the world has reacted much more strongly than it has to TB. "The fundamental problem is not how do we scare them into it, but how do we make people care. I think scaring them hasn't been working," said Chaisson.

Farmer, too, emphasized the ability of optimistic messages to inspire action. Some data suggest that a positive message of doing something to save lives has a greater chance of generating a response than a negative message, he said. The TB community has hampered itself by dwelling on the limited amount of funding that is available. The agenda needs to emphasize saving lives, not the idea that a disease is untreatable.

10

Developing and Strengthening the Drug Supply Chain for Drug-Resistant TB

Key Messages[a]

- The global need for anti-TB drugs is not currently being met.
- Barriers in the drug supply chain include small markets, a limited ability to forecast need, short shelf lives, a lack of financial incentives, and lax regulation that permits subpar treatment to reach patients.
- Public–private partnerships will be needed to overcome these barriers.
- Linking the anti-TB drug supply chain to existing systems, such as those for HIV or malaria, could facilitate access to anti-TB drugs.
- Data and information that underpin drug supply chains form their own information supply chains capable of tracking the risk of infection, preventing the emergence of DR TB, and improving patient follow-up.

[a] Identified by individual speakers.

Earlier in the same week that the workshop was held in Beijing, the IOM released a report on developing and strengthening the global supply chain for SLDs (IOM, 2013). Several presenters at the workshop also were involved in the preparation and release of that report, and they reviewed its most important messages and placed them in the context of the workshop's deliberations. As Mingting Chen, China CDC, pointed out, an affordable and quality-assured drug supply is crucial in national TB plans, and the issue is particularly relevant in China, which has manu-

facturers with the capability to produce almost all FLDs and SLDs. China also has developed the policy that all FLDs and SLDs are included in the country's basic drug list—meaning that medical insurance, not the patient, will pay for them. Mingting Chen explained that research revealed a bioequivalence of 80 percent for FLDs available on the market in China. To further improve the quality of drugs, China also is working to support local manufacturers of anti-TB drugs in their application for WHO prequalification. Mingting Chen observed that, although considerable efforts have been made to enhance the quality of anti-TB drugs in China, work remains to be done in collaboration with other countries and TB experts.

OVERCOMING BARRIERS IN THE GLOBAL SUPPLY CHAIN[1]

Successful treatment of TB requires changes throughout the health system, said Barry R. Bloom, Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, Department of Immunology and Infectious Diseases, Harvard School of Public Health. "If we had a new effective drug regimen for MDR TB," he said, "we couldn't get it where it needs to be." Failure to reach patients is the result not just of an inconsistent drug supply but also of missteps in the larger system. Although TB treatments had an 84 percent success rate in curing patients between 1995 and 2010 and mortality has fallen by 33 percent, Bloom pointed to the 5 million deaths from the disease during that same period as an indicator of how improvements to the system could yield great progress.

The IOM (2013) report on the global supply chain for SLDs shows that supply chains for drugs for other diseases, such as HIV and malaria, are more effective than those for TB drugs. Supply chains have many levels, Bloom pointed out, and their complexity can be challenging. They originate with the materials needed to produce the drugs and progress to manufacturing and formulation, storage, distribution, and use. The active pharmaceutical ingredient (API) is the most important component, and 80 percent of the APIs for TB drugs are made in China. The final product is distributed through warehouses, which source drugs for district or local clinics in various countries.

Many SLDs have only one producer, meaning that if a problem occurs with a batch, there is an immediate shortage of the drug. Japan's recent tsunami led to a shortage of isoniazid, not just in Asia or Africa but in the United States as well. The availability of APIs also has been limited

[1] This section is based on the presentation by Barry R. Bloom, Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, Department of Immunology and Infectious Diseases, Harvard School of Public Health.

because producers in China have not been prequalified by WHO to sell drugs internationally.

The need for anti-TB drugs is not being met, Bloom emphasized. In 2000, the GDF and Green Light Committee (GLC) were created as a pilot project to enable DOTS-Plus for both TB and MDR TB. However, treatment rates for MDR TB have remained low, and between 2000 and 2009, an estimated 1.5 million MDR TB patients died. In the past year, WHO has made changes to increase the number of suppliers of finished medicines and the number of approved APIs in an effort to reduce delays and lower prices. But the stipulation that essentially all drug procurement must go through the GLC is a bottleneck, Bloom said, seriously affecting the ability to get drugs to patients.

In the GDF system, requests from countries go to the GLC secretariat with technical support and advice from WHO. The GDF reviews a country's request to buy drugs. If the GDF approves the request, it sends the funds needed to purchase the drugs to the country, which then can make the purchase. Every step can take months to complete. "From the time of an order, it could take at least a year to get the drugs that were ultimately approved to the country that needed them," Bloom said. He called the duration of these delays "intolerable."

Barriers arise at several points in the supply chain, Bloom explained. The market for most SLDs is small, and the ability to forecast how much medication will be needed in the future is limited (see also Box 10-1). When suppliers overestimate, they lose money, so they are more likely to underestimate, which leads to a shortage of drugs. Many SLDs remain on the shelf for 2 years or more, and the companies that make them have few financial incentives to do so. The drugs also are costly, leading health ministries to focus on FLDs as a less expensive option. In addition, regulation is lacking, with the result that many drugs may have a low or below-standard dose of the API, and there is a potential market for fake and substandard drugs.

Reliable forecasting requires on-the-ground information, including the number of patients enrolled in every TB program, the number taking drugs, and the required lead times for manufacturing and shipping each drug. In addition, buffers are necessary to prevent breaks in the continuity of care. An 80 percent accurate forecast 2 months into the future is a worthwhile goal, Bloom said, with projections extending at least 24 months.

Forecasting requires functional information systems. Bloom suggested that linking to existing systems, such as those for HIV and malaria, could jumpstart an enhanced approach to TB treatment. Pooling requests from various countries and potentially aggregating procurement would provide better forecasts of the total numbers of needed drugs. A working capital fund also is critically needed to pay up front for production based on these forecasts. Members of pharmaceutical companies indicated at the 2012

BOX 10-1
The Challenge for Manufacturers[a]

The key problem for drug manufacturers, said Dan Collins, Global Health Programs and Access Department, Corporate Affairs, Eli Lilly and Company, is unpredictability of demand combined with low order volumes. Small manufacturers face high costs in getting drugs to patients, and obtaining approval for drugs is time-consuming. A majority of countries with a high burden of disease require both in-country regulatory approval and approval from WHO, increasing the time and cost required to bring a drug to market. Competition and forecasting, said Collins, will improve the market, allowing suppliers to plan for the future and eliminate stockouts, as well as reduce prices, while also enhancing the ability of governments and other funders to determine their budgets.

The public and private sectors need to partner to find solutions, Collins suggested, which could include technical support related to good manufacturing practices and quality assurance. Eli Lilly has technical expertise to bring to bear, he said, as well as experience building relationships with NGOs, government officials, regulators, and other organizations. That experience can be leveraged to find solutions.

[a] This box is based on the presentation by Dan Collins, Global Health Programs and Access Department, Corporate Affairs, Eli Lilly and Company.

IOM workshop (IOM, 2013) that they would be willing to help with forecasting and bundling shipments, Bloom added, but they have not been asked to do so.

Quality assurance could be handled by bar-coding packaging from qualified producers. Training is required to counter a lack of expertise in many countries in supply chain management and quality assurance. "We need to encourage the local production that becomes global production," Bloom said, "and with that, strengthen the vigilance and the quality-control regulation to be sure that what is being taken by patients is the highest quality possible."

Bloom also proposed establishing a partnership between private and public organizations. Neither sector has all the tools necessary, he said, but a partnership between the two could lead to significant supply chain improvements. Private-sector pharmaceutical companies have mastered many of the necessary components of an efficient supply chain, but the market for most TB drugs is too small to interest them. A new mechanism

is necessary, he said, one that can engage the private sector, manufacturers, distributors, governments, and donors.

Currently, Bloom added, even if drugs are prequalified by WHO, 27 countries must go through additional national regulatory processes. Quality-assured drugs for malaria required 9 to 15 months to be revalidated in some African countries. That time must be shortened, Bloom said. Innovative financing mechanisms could provide more money for TB drugs, for which funding is lacking for both drug-susceptible and drug-resistant forms of the disease. The IOM (2013) report suggests many mechanisms for addressing financing issues, including advance product commitments and models for negotiating lower prices.

Making the necessary changes, Bloom concluded, will require strong and visionary leadership. It also will require continuing education, information sharing, and behavior change. The Affordable Medicines Facility for Malaria (AMFm) program included a component on information and behavior change, and the countries that failed to meet the benchmark evaluations failed in the information component. "We need to think of a much simpler and more efficient way of presenting the complexities of TB and the supply chain," Bloom concluded.

A SYSTEMS PERSPECTIVE ON THE GLOBAL SUPPLY CHAIN[2]

A systems perspective on the global supply chain is needed to ensure an uninterrupted supply of quality-assured drugs when and where when they are needed, said Rifat Atun, Imperial College, London. For many diseases, not just TB, the United Nations (2012) has reported that the availability of essential medicines is low worldwide. In some areas, data indicate that the average availability of drugs used to treat common conditions is 51.8 percent and 68.5 percent, respectively, in public- in private-sector health institutions—too low to cover affected populations. Clearly, weak supply chains hinder access to essential medicines and technologies and need to be strengthened, said Atun.

The first step toward improving supply chains, Atun suggested, is to understand them in their entirety, as many discussions have focused on selected components of supply chain management systems. At their core, most supply chain management systems comprise a series of manufacturers, along with a storage facility that is central or belongs to a specific region or district. Drugs are moved from storage to clinics and patients. In most countries, they also reach patients through private entities, distributors, and retailers. In many systems, the manufacturers that produce the API may be

[2] This section is based on the presentation by Rifat Atun, Professor of International Health Management, and Head, Health Management Group, Imperial College London.

different from those that produce the final drug. Hence, additional manufacturers farther upstream in the supply chain create the starting materials for a drug's final form, whether it is an injectable or a pill.

Even before manufacturing begins, however, drugs must go through a series of hurdles. R&D, which includes several phases of clinical trials, product approval through regulatory authorities, and registration of the drug, can take 10 to 12 years and is characterized by attrition at every step. Of 100,000 entities that enter the discovery process, only 1 drug on average makes it to the market.

Supply chains also take many different forms. Some are automated, allowing patients to order drugs on the Internet and receive them in the mail. In other cases, health workers literally carry drugs to patients. Where supply chains do not work, patients may be brought to the source of drugs instead of the other way around. A problem anywhere in the supply chain can prevent a drug from reaching the end user.

Even when supply chains are in place, a mismatch between demand and supply can occur. If forecasts of need are unpredictable, as is the case with drugs for MDR TB, orders fluctuate, and manufacturers cannot develop production plans or adjust for future demand. The result is periods of supply–demand asymmetry and fluctuation in drug prices.

Both "push" and "pull" mechanisms are necessary to improve the supply chain for SLDs, said Atun. Push strategies might include tax breaks for R&D, public–private drug development partnerships, and fast-track approval for new products, as well as direct funding for R&D from governments. Examples of potential pull strategies include innovative financing mechanisms (such as integrated international financing institutions) and innovative financing instruments (such as advance market commitments, volume guarantees, and social impact bonds). Finally, and critically, platforms to enable functionality—appropriate regulatory environments, strong health systems, and a mix of public and private delivery of services—also are necessary. A successful systems approach, Atun explained, would combine push and pull strategies with such enabling platforms to get drugs and diagnostics to patients as efficiently as possible.

Atun offered several examples of novel supply chain management systems for drugs for other diseases. AMFm, established by the Global Fund, was successful in reducing prices of innovative malaria drugs by providing indications of increased demand while cofinancing the purchase of certain volumes, thereby reducing the use of ineffective generic malaria drugs previously preferred by patients as a less costly alternative. The Global Fund also worked to overcome issues of fragmented procurement for antiretroviral drugs by establishing voluntary pooled procurement and instituting a transparent Price and Quality Reporting (PQR) mechanism for all the key drugs included in the regimens commonly used to treat AIDS. The principal

recipients of Global Fund grants received technical support through a consortium with expertise in supply chain management and pooled procurement to help simplify the procurement and supply chain management process. PQR data, available on the Global Fund website and verified by local Global Fund agents, capture every funded transaction. These data are accessible to the public, grant recipients, and partner agencies. Price transparency made it possible to reduce prices, Atun said, with 91 percent of transactions falling to or below international reference prices within a few years of implementation of the PQR system, and more consistent prices overall across countries receiving Global Fund financing.

To introduce improvements at all points along the supply chain so as to enhance access to effective medicines, a 10- to 20-year view is necessary. "We need to create an environment where innovation is encouraged and innovations are adopted by countries and health systems," Atun said. Empowered decision makers and institutionalized processes also will enhance the functioning of the supply chain.

INFORMATION IN THE GLOBAL SUPPLY CHAIN[3]

"Information is a public health intervention," said Dale Nordenberg, Chief Executive Officer, Novasano Health and Science. Data and information supporting a global supply chain make up their own supply chain. Data require a functional, comprehensive supply chain to support the drug supply and public health programs. A good information supply chain can track the risk of infection, prevent the emergence of DR TB strains, and improve contact tracing and follow-up. Without attention to these informational supply chains, suggested Nordenberg, "we'll build technologies, and they will function in specific locations, but never really support a robust flow of data and information."

Information distribution faces many challenges, particularly in the context of rural health care. Many areas lack a standardized process for patient management, and record keeping varies among locations and patients. Transportation is unreliable, and communication problems are common. More than 50 percent of people in rural areas fail to seek medical care. Care is delivered in a wide range of places, Nordenberg pointed out, but each country needs to identify the critical information points. If the SLD supply chain depends on creating technological capabilities from the ground up in every country, establishing a comprehensive system will take far too long.

An information supply chain uses data as raw material, synthesizing the data and transferring them from place to place. Human resources are

[3] This section is based on the presentation by Dale Nordenberg, Chief Executive Officer, Novasano Health and Science.

necessary to drive the development, maintenance, and operations of this supply chain, and standard operating procedures keep the system functioning smoothly. There exist many different approaches to managing the information supply chain, and these approaches can be integrated to best serve the needs of a particular sector.

Electronic medical records (EMRs) are central to many information systems. They provide the ability to track patients, their treatments, and the results of those treatments. To create a robust information system, as many EMRs as possible are needed, Nordenberg said. The key attributes of the EMR are its collaborative development and open-source nature. The data are designed to be easily managed, supporting reports to WHO and application to public health problems, as well as forecasting of the need for drugs. The EMR also can be designed with mobile devices in mind for ease of use. However, Nordenberg cautioned against ignoring the peripheral systems that facilitate tracking efforts.

Core variables contained in an EMR include demographics, drug regimen, treatment status and outcome, laboratory data, any adverse effects, and socioeconomic factors. Nordenberg suggested that teams could quickly assess where TB patients are being treated in a specific country and where data are needed to build that country's capacity to transfer and use information.

Nordenberg recommended a two-phase solution, beginning with critical information points and moving toward the development of more robust solutions over the long term. Measurable performance metrics are critical to a successful information system, Nordenberg added. Improved drug coding standards and standardized reporting elements for drug stocks and status are necessary, as well as technology planning that looks across diseases, avoiding a silo-based approach. Finally, Nordenberg emphasized the importance of tracking activity across various drugs and programs, including not only SLDs but also clinical care, infection control, and epidemiological activity.

LAUNCHING NEW ANTI-TB DRUGS[4]

Xian Janssen Pharmaceuticals is preparing for the launch of a new drug to treat MDR TB, explained Oskar Slotboom, Head, Vaccine and Infectious Diseases, Xian Janssen Pharmaceutical Ltd., Johnson & Johnson. The process from discovery to market authorization has already taken 12 years. From a business point of view, the fact that only a few patients can be reached, together with significant drug funding issues and a lack of forecasting ability, makes launching new drugs for MDR TB a daunting

[4] This section is based on the presentation by Oskar Slotboom, Head, Vaccine and Infectious Diseases, Xian Janssen Pharmaceutical Ltd., Johnson & Johnson.

proposition for companies. Companies also are concerned about issues with adherence to drug regimens, as lack of adherence can lead to the buildup of resistance and thus compromise the future utility of a drug.

Janssen developed its drug without expecting commercial success. If both large and small companies saw commercial potential in developing new drugs for MDR TB, they would invest more in innovation, and a more diverse market would emerge, Slotboom continued.

Janssen is trying to ensure that patients can be reached by getting its drug registered in more than 30 countries and expects to meet WHO guidelines for prequalification. The company is concerned about appropriate use and hopes to avoid contributing to the emergence of resistant TB strains in the future by using a strategy called rational distribution, whereby it limits where the drug will be made available to avoid issues arising in how the drug is administered. This strategy entails working primarily with national programs and certain private clinics, Slotboom explained, as well as supporting current efforts to educate health care professionals.

For this drug, some supply chain issues will be less severe than is the case with many other drugs, Slotboom said. The company has been working to bring its production of the drug up to high capacity and can do so quickly. It also is working with global companies and organizations with experience in the MDR TB field to address potential supply chain problems.

Slotboom suggested that treating more patients may be the only way to make significant improvements in the industry's overall supply chain. The current volume of drugs used in MDR TB treatment is so small that any supply chain system will be very inefficient and cumbersome. By contrast, the GAVI Alliance ("GAVI") and UNICEF (United Nations Children's Fund), for example, handle more than 100 million doses of many vaccines and drugs used to treat other diseases through fairly efficient supply chain organizations. A larger volume of drugs also would facilitate forecasting and advance market commitments. Slotboom argued that shifting more money to the development of rapid MDR TB diagnostic capabilities would contribute to an increase in drug volume.

Finally, Slotboom discussed the problem of "marketing" the disease, which he said has helped gain financial support to combat other diseases, such as AIDS and polio. People like Bill Gates, he pointed out, have lent this work considerable momentum. Attracting such support "requires a clear and simple message that people can say yes to," he cautioned.

Other potential drug candidates in late-stage development give cause for optimism, suggested Slotboom. He concluded by emphasizing the need for continued investment by both the public and private sectors if this potential is to be realized.

11

Embracing a New Vision for Research

Key Messages[a]

- TB is responsible for an enormous burden of human disease yet is still understood poorly at a fundamental level.
- High-quality clinical research in developing countries is possible; field-based clinical and basic research can impact diagnosis, care, management, and vaccine development.
- Sequencing of TB genomes linked to patient histories can reveal patterns of drug resistance, identify molecular markers and pathways for new and improved drugs and diagnostics, and provide key datasets for molecular epidemiology and surveillance efforts.
- The integration of epidemiology with systems biology is creating a "systems epidemiology" that can provide a comprehensive view of infection, disease progression, and transmission.
- Meta-analyses of data gathered from many sites can answer questions that cannot be answered with data from a single site.

[a] Identified by individual speakers.

Five speakers at the workshop discussed new forms of TB research that could have a dramatic effect on TB prevention and treatment. New technologies and innovative analytic methods offer opportunities not available with traditional approaches.

CREATING A SYNERGY OF DISCOVERY AND DELIVERY OF CARE[1]

Around the year 2000, Anne E. Goldfeld, Harvard Medical School and GHC, started to see wasting and dying caused by AIDS in Cambodia, which previously had been largely spared from that epidemic. Many children were taking care of their dying parents, and others were themselves infected. "We were overwhelmed about how to handle this," said Goldfeld. From private sources, she and her colleagues were able to obtain the funds needed to keep 100 people alive for 1 year. They also began conducting research through the Comprehensive International Program for Research on AIDS (CIPRA), partly because they knew this work would help get AIDS drugs into the country. And they convinced the photographer James Nachtwey to come to Cambodia to document the country's joint epidemic of AIDS and TB, helping to shed light internationally on this problem, which was underappreciated at the time. Goldfeld noted that between a quarter and a half of the 30 million people with HIV infection who have died have actually died of TB, which is curable even in a setting with a high prevalence of AIDS.

Goldfeld and her colleagues have been performing hypothesis-driven research in Cambodia to understand the molecular basis of TB's natural history and to develop operational models for treating the disease, particularly in patients coinfected with HIV. TB and HIV infection each result in a host immune response, which in turn boosts the natural progression of the other pathogen. TB infection usually occurs first, followed by HIV infection, progression to AIDS, and extraordinarily high mortality, particularly when the CD4 level dips below 200. (Goldfeld pointed out that reinfection with TB also is very common in immunosuppressed HIV positive individuals.) When Goldfeld's team began their research, the international recommendation from WHO was to start antiretroviral therapy for HIV at 2 months following diagnosis. Some data from retrospective studies indicated that an earlier start to therapy produced better outcomes, but drug–drug interactions were a concern for coinfected patients—for example, rifampicin speeds up the cytochrome P450 system of the liver, which increases side effects and the burden of taking medicines.

Goldfeld and her colleagues proceeded to explore the hypothesis that early initiation of antiretroviral therapy would increase survival in coinfected patients despite a more complex initial clinical management. With the support of the Agence Nationale de Recherche sur le SIDA, the NIH Division of AIDS, and the Institut Pasteur in Cambodia, the research team, together with the Cambodian Health Committee, developed five clinical sites in

[1] This section is based on the presentation by Anne E. Goldfeld, Professor of Medicine, Harvard Medical School; and Co-Founder, GHC.

Cambodia, which at that point had no real research infrastructure. The first patient was recruited to the trial in 2006, and recruitment ended in 2009, by which time AIDS drugs were available in Cambodia through the Global Fund. A total of 661 patients were randomized, about half to the early and half to the late arm. Most were culture positive. Their CD4 count averaged 25—"unbelievably low," according to Goldfeld—and their BMIs were very low as well. Fewer than 2 percent of patients were lost to follow-up, and fewer than 1 percent of almost 9,000 protocol visits were missed. The project was called CAMELIA, for Cambodian Early versus Late Introduction of Antiretrovirals, and the results were published in 2011 in the *New England Journal of Medicine* (Blanc et al., 2011).

The findings from this research were "stunning," said Goldfeld. The early arm resulted in a 34 percent reduction in mortality. By using drugs that were already available, death rates were markedly reduced. "Obviously we need many new drugs, but one can do better with what one has in hand," Goldfeld asserted. She added that having MDR TB resulted in an eightfold increased risk of death, partly because of delays in diagnosis.

The research also gave the team an opportunity to learn about the impact of TB on the reconstitution of the immune system during antiretroviral therapy. (Goldfeld noted that securing funding to pursue this basic scientific question proved to be extremely difficult, and the research was possible in part because of a private donation from the Annenberg Foundation.) Goldfeld described some of the initial results of this research, which are elucidating some basic principles involved in the immune response to HIV and TB and which were still being analyzed at the time of her presentation.

The research conducted by Goldfeld's team revealed that, on a worldwide basis, early antiretroviral therapy could save as many as 150,000 of the 450,000 lives lost to combined HIV and TB infection. The results of the research have already affected national policy in Cambodia, and a WHO follow-up recommendation is expected.

Nobody believed that a high-quality international clinical trial was possible in a setting such as Cambodia, said Goldfeld, but this assumption was proved wrong. She emphasized that the combination of basic science and a clinical network is a powerful way to learn more about TB and HIV infection. It also had numerous other benefits, including vastly improved research infrastructure and capacity. Goldfeld concluded by noting that field-driven clinical and basic research can impact diagnosis, care, management, and vaccine development.

NEW TOOLS TO FACILITATE TB RESEARCH[2]

Maria Y. Giovanni, Director, Office of Genomics and Advanced Technologies; Assistant Director, Microbial Genomics and Advanced Technology; Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH, explained that NIAID funds basic research along with the development of new drugs, diagnostics, and vaccines. In the area of TB, it funds basic research and natural history studies in addition to drugs, diagnostics, and vaccines. NIAID has been taking advantage of new sequencing technologies by investing in genomics to provide resources and tools, including drug discovery and drug development tools, for researchers. For example, three Genomic Sequencing Centers for Infectious Diseases create databases, tools, 3-D structures, protein clones, and predictive models that are freely distributed to the scientific community. NIAID also has developed a research agenda for MDR and XDR TB (NIAID Working Group, 2007).

In 2012, NIAID and international collaborators launched the Large-Scale TB Genome Sequencing Project. Using high-throughput, next-generation sequencing technology along with bioinformatics analysis and tools, the project has the goal of sequencing more than 1,000 TB strains from Korea, Russia, South Africa, Uganda, and other countries. These TB genomes will be linked to patient histories to advance understanding of genetic patterns of drug resistance, identify molecular markers and pathways for new and improved drugs and diagnostics, and provide key datasets for molecular epidemiology and surveillance efforts. NIAID also is a founding member of the TB International Genome Consortium, which is investigating drug resistance in different TB strains.

NIAID has developed a database called the Pathosystems Resource Integration Center (PATRIC) that has a strong focus on TB. To build synergy, PATRIC has deidentified genomic as well as many other kinds of data, including data contributed by members of the TB community. NIAID has been emphasizing the collection of clinical data and metadata to enhance the richness and utility of the data it provides. Almost every string sequenced in PATRIC has associated clinical data and metadata that are available for use.

The Institute has made a major commitment to systems biology, which makes it possible to combine different kinds of datasets and construct predictive models. Through this work, many gaps in understanding of the regulatory networks for TB have been filled in the past few years, with

[2] This section is based on the presentation by Maria Y. Giovanni, Director, Office of Genomics and Advanced Technologies; Assistant Director, Microbial Genomics and Advanced Technology; Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH.

the number of demonstrated protein-gene interactions increasing almost 17-fold since 2008.

To reduce the risk and expense of drug development, NIAID offers services, provided by contractors, to academic and industrial investigators worldwide. The objective is to facilitate research at all stages—from basic research through clinical applications—by developing critical information needed to move a product along the product development pathway. In addition, the Institute provides organisms, reagents, assays, animal models, in vitro and in vivo screening for antimicrobial activity, and candidate therapeutics.

Finally, Giovanni briefly mentioned NIAID's support for diagnostics development. The goal is to develop integrated diagnostic platforms that are rapid, inexpensive, easy to use, sensitive, and specific for detecting multiple targets to support diagnosis of infectious diseases, determination of antimicrobial resistance, and monitoring of treatment and prevention.

TBRESIST: A GLOBAL CONSORTIUM FOR WHOLE-GENOME SEQUENCING OF DRUG-RESISTANT TB[3]

Comas and Gagneux (2009) have suggested that control of DR TB will remain a formidable challenge for many years to come unless two new technological developments are rapidly applied, noted Gail Cassell, Harvard Medical School and Infectious Disease Research Institute. The first is high-throughput genomic technologies, which have already contributed greatly to the understanding of TB epidemiology, comparative genomics, evolution, and host-pathogen interactions. Cassell listed several examples of advances these technologies have produced. They have

- demonstrated the importance of ongoing transmission and the existence of drug resistance even in places where little TB treatment has taken place;
- demonstrated that the mycobacterial genome has more genomic plasticity than expected, as well as shown the evolution and geographic distribution of different strains;
- provided the first rigorous evidence that previous exposure to TB does not protect against reinfection, a finding that has major implications for vaccine development;
- allowed differentiation of patients who relapsed because of treatment failure from those reinfected with a different strain;
- enabled pragmatic public health efforts, such as detection of outbreaks and ongoing TB transmission; and

[3] This section is based on the presentation by Gail Cassell, Visiting Professor, Harvard Medical School; and Vice President of TB Drug Discovery, Infectious Disease Research Institute.

- pointed to possible associations between genomic content and disease severity.

The second critical technological development cited by Comas and Gagneux entails the integration of epidemiology with systems biology to create a new "systems epidemiology." This integrated field would systematically link genomic data with other forms of "omics" data and with clinical data to provide a systematic view of infection, disease progression, and transmission.

TBResist is a global consortium for whole-genome sequencing of DR TB strains that seeks to both take advantage of and advance these two technological developments. It has several major goals:

- to better address DR TB and such comorbidities as HIV infection and diabetes;
- to better understand latency, including the incidence and effects of mixed infection and the characteristics of replicating versus non-replicating organisms;
- to better predict the future disease trajectory of disease; and
- to develop new tools, including drugs, diagnostics, and vaccines.

Achieving these goals will be possible only by aggregating data from thousands of patients and thousands of strains, as is being done in other disease areas, said Cassell. The consortium will bring together many diverse investigators who are willing to share their data and build large databases of genomic data from well-characterized patient populations.

The founding members of the consortium are the Laboratory Information for Public Health Excellence, NIAID, the Broad Institute, and IBM, which is supplying its powerful HIV data-mining tool EuResist, along with bioinformaticists who specialize in mining data from medical databases. Many other public and private groups also have joined the consortium, including several from BRICS countries. A strong interdisciplinary team is building a mathematically and statistically robust analytical framework to make sense of the data deluge. TBResist sequencing centers are located at the Broad Institute and in China, Russia, and Taiwan.

The consortium plans to publicly release all of the sequence data, including RNA data, as rapidly as possible. For the clinical data and metadata, each participant must have a data sharing and release plan, although the release can be delayed up to 9 months or until publication. Patrick Tao Li, Scientific Representative, BGI (formerly Beijing Genomics Institute), described his organization's collaborative efforts to develop methods for TB diagnostics and DST (Box 11-1).

BOX 11-1
Investing in TB Sequencing[a]

BGI (formerly Beijing Genomics Institute), which has been extensively involved in DNA sequencing for plants, animals, and human diseases, is making a major investment in TB, said BGI's Scientific Representative, Patrick Tao Li. BGI uses multiple generations of sequencing to ensure validated sequences, and then uses these data to find single nucleotide polymorphisms relevant to resistance. BGI also is analyzing the transcriptome from TB samples and DNA methylation, which affects gene expression.

In collaboration with other research groups from around the world, BGI is using these data to develop methods for diagnosing TB and testing for drug resistance. A large portion of these data is stored in the BGI cloud so researchers with permission can access BGI's supercomputer through their laptops to analyze data and make contributions to the project.

[a] This box is based on the presentation by Patrick Tao Li, Scientific Representative, BGI (formerly Beijing Genomics Institute).

META-ANALYSIS[4]

Meta-analyses provide a way to pool information gathered from many sites to answer questions that cannot be answered with data from a single site, said Kathryn DeRiemer, Associate Professor, Department of Public Health Sciences, School of Medicine, University of California, Davis. She described a meta-analysis with which she was involved that looked at treatment regimens and patient outcomes for more than 9,000 patients (Ahuja et al., 2012). The study pooled data from 71 co-authors and 32 countries. Earlier reviews had identified 93 studies conducted prior to 2009 that included at least one MDR TB case. Of these studies, 26 were excluded because they represented the same or overlapping cohorts. Other studies were excluded because the original investigators no longer had access to the data or did not have data on DST, or for other reasons. Patients were excluded who had XDR TB or exhibited only extrapulmonary TB, or for whom information on treatment outcomes was lacking.

[4] This section is based on the presentation by Kathryn DeRiemer, Associate Professor, Department of Public Health Sciences, School of Medicine, University of California, Davis.

The objectives of the meta-analysis were to assess the impacts of specific drugs, the number of drugs used, and the duration of treatment on the clinical outcomes of patients with pulmonary MDR TB. Once approvals had been obtained from each of the local ethics boards at the participating institutions, deidentified data were sent to a central data center at the Montreal Chest Institute of McGill University. The meta-analysis investigators consulted extensively with the authors of the original studies to ensure that the data were accurate and reflected the defined outcomes.

The meta-analysis estimated the odds of treatment success, defined as cure or treatment completion versus treatment failure or relapse; combinations of treatment failure, relapse, and default; and combinations of treatment failure, relapse, death, and default. Random-effects multivariate logistic regression models were used to estimate odds ratios and confidence intervals.

Of the 9,153 individuals with MDR TB in the study, 66 percent were sputum smear positive, and 52 percent had cavitary lesions. A number of drugs were used to treat these MDR TB patients. Some of these drugs were those that were available at the time the patient required treatment. No set regimen was followed in each of the sites, and limited information is available on the specific regimen followed by each patient over long periods of time.

The overall treatment success rate was 54 percent. Fifteen percent of patients in the study died, which translates to more than 1,300 deaths. A substantial number—23 percent—defaulted, transferred out, or had unknown outcomes, a concern with respect to the transmission of MDR TB.

Use of later-generation ethionamide, ofloxacin, and quinolones or a related drug was associated with treatment success compared with treatment failure, relapse, or death. In the intensive phase of treatment, MDR TB patients who were treated with four or more effective drugs (based on DST) had better treatment outcomes. In the continuation phase, use of at least three effective drugs was a predictor of treatment success.

For the initial treatment phase, most patients underwent 7 to almost 9 months of therapy. The total duration of treatment was about 18 to 22 months for these MDR TB patients.

This study represents the first attempt to pool data on MDR TB patients from many different countries and different sites and studies, which created some limitations:

- Different field studies used different guidelines and case management strategies, depending on the country and clinical practice.
- The availability of SLDs varied among studies.
- Specimens were not available for further analysis, such as additional DST and genome sequencing.

Nevertheless, this research points to the potential of a future prospective study looking across different sites, with standardized data collection and multiple specimens per patient at different points during therapy.

From a clinical and program perspective, said DeRiemer, treatment consists of at least four steps: (1) screening/testing, (2) diagnosis, (3) treatment, and (4) outcome. In the past, the goal has been to develop guidelines for good clinical practice that provide guidance on these steps, with the assumption that these guidelines would be appropriate for all cases everywhere. But MDR TB treatment is now taking much longer than it has in the past, which DeRiemer ascribed to the continuous nature of *M.tb.* infection. The goal of the pathogen is to multiply and transmit itself to other people. As a result, the bacterial burden in an individual may be increasing over days, weeks, months, years, or a lifetime. Therapy produces a selective pressure, which leads to mycobacterial diversification through mutations and genomic deletions. The goal of treatment therefore must be to reduce or eliminate the bacterium by the time treatment is completed. Accomplishing this goal requires asking questions about the pathogen burden, heterogeneity, and diversification.

DeRiemer concluded by urging collaborative prospective human studies with multiple time points for specimen and data collection. She also recommended incorporating new tools in these studies that can illuminate how mycobacterial changes such as mutations affect treatment outcomes.

12

What Will Be Required to Achieve Zero Deaths from TB?[1]

Key Messages[a]

- The biomedical approaches and delivery systems used to attack TB are not being optimized.
- Moving from a minimalist approach to an "optimalist" approach, in which TB cases are identified rapidly, active case finding is performed, infection control is implemented to reduce transmission, and patients are treated based on the results of rapid DST, could yield dramatic progress.
- The BRICS countries have a unique opportunity to take a leadership role and scale up diagnosis and treatment of TB and MDR TB, in addition to the socioeconomic interventions that reduce poverty and enhance TB control efforts.
- The intentions of BRICS country health ministers, as reflected in the Delhi Ministerial Communiqué (see Box 1-4 in Chapter 1), reveal promise in the potential future leadership of the BRICS to combat MDR TB.

[a] Identified by Salmaan Keshavjee, Director, Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School.

[1] This chapter is based on the presentation by Salmaan Keshavjee, Director, Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School.

In the final session of the workshop, Salmaan Keshavjee, Harvard Medical School, presented his views on what will be required to achieve zero deaths from TB. His talk revisited many of the topics discussed during the workshop and provides a useful look back on the meeting.

WHY HAS CONTROLLING TB BEEN SO DIFFICULT?

Rates of HIV infection and deaths from AIDS have dropped markedly in recent years, as have deaths from malaria. During this same period, however, death rates for TB have been nearly static, declining only about 1 percent per year. The only reason TB mortality may appear to be declining is that HIV-infected patients dying from TB are sometimes classified as "non-TB deaths." This is a classification artifact and does not represent the true impact of the disease or the unmet need for treatment, said Keshavjee, who noted that, although effective treatment regimens for TB have been available since the early 1950s, 1.5 million to 2 million people still die annually from the disease. "Overall, we have not been successful with the tools that we have been using," said Keshavjee.

The reason for this lack of success is that optimal biomedical approaches and delivery systems have not been used to attack the disease. The DOTS approach, for example, is a minimalist, not an optimized strategy. Although it has saved millions of lives by standardizing treatment for TB, it was never designed to address drug resistance, a phenomenon that has existed since the use of the first anti-TB drugs. According to Keshavjee, "years of advocating an approach that overlooked resistant strains was a mistake." DOTS, which requires having a regular supply of high-quality drugs, has had great benefits, but the program also has several limitations:

- It lacks integration with country procurement systems.
- It includes neither SLDs nor drugs for adverse events.
- The DOTS strategy does not include active case detection and relies on patients appearing when they are sick.
- The program has no strategy for latent disease, despite research showing that treatment of latent disease yields mortality and transmission benefits.
- A sole focus on short-course chemotherapy as a panacea has curtailed the development of appropriate adjunct therapies, such as surgery, for patients with advanced disease.

Diagnosis with sputum smear microscopy also has been suboptimal for patients with smear-negative or extrapulmonary TB. It has low sensitivity in patients with paucibacillary disease, such as pediatric populations or people infected with HIV, and is incapable of identifying resistant strains.

Although sputum microscopy is low cost and can be performed in remote areas, it is not well suited to addressing some of the principal drivers of the TB epidemic over the past two decades, Keshavjee said.

Keshavjee noted further that standardized recording and reporting have led to much greater accountability in TB control worldwide. However, the systems used have been unable to capture complex data, such as those related to MDR TB, coinfection with HIV, and diabetes as a comorbidity.

Finally, Keshavjee suggested that a minimalist approach has led to a lack of focus on transmission and infection control and thus a lack of emphasis on the appropriate design of facilities and systems to prevent transmission. Particularly with MDR TB, strains of which have mistakenly been thought to be too weak for transmission, the lack of infection control has contributed to the spread of the disease. A minimalist approach also has led to limited engagement with the private sector, not only for drug delivery but also for drug R&D. Clinical and delivery systems have been separate from other health services, so that TB screening has not been conducted as a routine part of health care.

"The paradigm we have been working within has been very inflexible," Keshavjee said. "It has not been able to respond to change in light of new evidence." The paradigm now needs to be revised, he asserted.

HOW CAN PROGRESS BE RADICALLY IMPROVED?

Keshavjee urged moving from a minimalist approach to an "optimalist" approach. He invoked the acronym FAST used earlier in the workshop by Edward A. Nardell, Brigham and Women's Hospital, Harvard Medical School, which stands for

- ***F***ind TB cases through rapid diagnosis.
- Perform ***A***ctive case finding by focusing on cough surveillance.
- ***S***eparate safely and reduce exposure through infection control.
- ***T***reat effectively based on rapid DST.

Keshavjee noted that, in general, the case detection rate for all TB patients has been improving in recent years. Yet, an estimated one-third of all TB cases—more than 3 million people—are not detected each year. Addressing the first of the above steps, Keshavjee added that HIV and TB have been driving each other's epidemics for years. Yet, the percentage of HIV positive people screened for TB remains low on a global level. Although some countries do perform universal screening of those infected with HIV for TB, "on a global level, every person with HIV should be screened," Keshavjee said. Similarly, children make up somewhere between 10 and 30 percent of TB patients, but diagnostics for children are poor and

often are not employed. More appropriate diagnostics and case-finding strategies for children remain "a dire need," said Keshavjee.

The workshop clearly demonstrated potential solutions to these problems, Keshavjee said. One solution is to develop true point-of-care tests for TB and DR TB. The perfect test is not essential, said Keshavjee. For example, the rapid strep test is accurate just 75 percent of the time, but it has a crucial benefit: It can be performed at the point of care. When people must walk hours to a clinic or spend precious resources on transportation, they need to be diagnosed quickly and started on treatment.

The performance of TB programs also can be improved. The percentage of newly diagnosed TB patients who receive DST remains below 10 percent worldwide and is only about 30 percent even in Europe. Even the percentage of retreatment cases receiving DST is below 10 percent, despite the greater likelihood of drug resistance in these cases.

Improvement also can be achieved by realizing that with molecular drug susceptibility tests, one size does not fit all. Tests to determine SLD resistance reliably therefore need to take variation into account. Within countries there exist pockets of resistance that are different, which means that diagnostics need to be applied in a calculated way.

A further area for improvement is integration of TB programs with other parts of the public and private health systems. For example, Keshavjee described a project funded by the Stop TB Partnership's TB Reach initiative in which Pakistani health care workers at private general practitioner clinics screened patients for TB and referred them for sputum smear microscopy and X-rays. During the course of just 1 year, the case notification rate for all forms of TB almost quadrupled. Many of the patients were smear-negative but proved to have cavities when X-rayed.

With respect to treatment, Keshavjee stressed that when patients are started on an effective treatment regimen, they become less infectious. The optimal way forward is therefore to give people the right treatment so that high resistance does not develop. Data from South Africa indicate that standardized therapy has drawbacks because of the variation that exists even on a local scale.

MDR TB is still TB, Keshavjee emphasized. It is transmitted through the air, which is why it spreads. Universal access to care may be extremely difficult to achieve, but it must be a priority. Keshavjee suggested that the way to achieve universal access to care is through community-based care. "Patients have lives, they have kids, they can't be locked up for 2 years," he said. "It's unreasonable for us to expect that from people, and we don't have the beds or capacity to do that anyway." Ambulatory care and community-based approaches provide a way to treat large numbers of patients rapidly, safely, and outside of congregate settings. Community-based care that works takes the needs of patients into account. It provides

wraparound services such as provision of food and other enablers that help patients complete treatment successfully.

For patients to be placed on an effective regimen, a reliable, affordable supply of quality-assured drugs is essential. Improved supplies of SLDs would be a major achievement, said Keshavjee, but the drugs need to be part of a comprehensive package that includes ancillary drugs for adverse events, equipment required to deliver the drugs, and other delivery mechanisms. Today, this system is centrally run, which has some benefits, but there also are benefits to having a variety of nodes in a supply chain system, which can improve efficiency and effectiveness. In this way, the demand for and supply of drugs can be more evenly matched so that all the drugs that are made are used.

Keshavjee next turned to preventive therapy for TB, which he acknowledged can be a contentious subject. But given the challenge of dealing with active cases, preventive efforts can produce benefits, especially in areas with high rates of latent disease. Studies conducted in the 1960s showed that isoniazid therapy can have a protective effect that persists over two decades, and possibly for a lifetime. Such therapy also has been shown to be highly effective in preventing mortality among people living with HIV. In addition, prophylaxis for contacts of MDR TB patients—an area of inquiry that remains to be sufficiently explored—can be important, especially for children, for people infected with HIV, or for contacts. Keshavjee suggested that preventive therapy should begin by focusing on those at highest risk of developing active TB, such as individuals exposed to silica dust, patients treated with immune modulators such as steroids, diabetics, and smokers.

Addressing adjunct therapies, Keshavjee cited the need for further research to determine their effectiveness. Potential approaches include the use of autologous mesenchymal stromal cells, other immunomodulators or anti-inflammatories, or therapeutic vaccines. Mortality rates are very high among people with XDR TB and those who have failed treatment, which argues for considering other therapies.

Keshavjee next noted that effective treatment requires not only having the right drugs but also optimizing care delivery systems or platforms. Even when the right drugs are available, they may not be used enough or appropriately for patients to be cured. In many places, an implementation gap hinders treatment delivery, and this is an area requiring much greater focus, particularly for drugs that need to be delivered for extended periods. Keshavjee acknowledged that the delivery of treatments can be daunting. Many of the countries with the highest burden of MDR TB have relatively weak health care systems. In such cases, mechanisms to fill the implementation gap are a priority.

Taking a broader view, Keshavjee emphasized that TB is a disease of poverty, and ameliorating poverty can have an enormous effect on its

control. In addition to biological factors, food security and consumption patterns, health-seeking behaviors, housing quality, ventilation, and many other factors contribute to infection and active disease. Socioeconomic interventions can reduce the exposure to these risk factors, lower the burden of disease, improve screening, and boost treatment success. Even eliminating fees for patients can increase the use of public and private health care. "TB is a biological phenomenon, but it's also a social phenomenon," said Keshavjee. As an example, he briefly described a study of cash transfers and microfinance interventions for TB control (Boccia et al., 2011).

Similarly, investments in national TB programs in the public sector, while not a complete solution, can produce higher case detection rates and lower TB incidence, prevalence, and mortality (Akachi et al., 2012). Strengthening the public sector also can improve private-sector care through increased monitoring and engagement.

Reflecting on a white paper developed to support the first workshop in the IOM series, Keshavjee indicated that the system for providing international technical assistance is currently inadequate. The system needs to be transformed to do better at drawing on the experience of successful regional MDR TB treatment programs; to include the provision of onsite, long-term technical assistance; and where necessary, to involve onsite implementation teams (Keshavjee and Seung, 2008). The underlying message is that countries need strong support, such as was provided by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), if their TB programs are to succeed, asserted Keshavjee.

Keshavjee reported that at a recent meeting in Cambridge, Massachusetts, a group of researchers, administrators, policy makers, and advocates discussed how to move forward with TB control. The group decided that it needed an orienting principle at the dawn of the 21st century, when people are still dying of a treatable disease. The group decided that the world needs to strive for "zero deaths from TB." It signed a document called the Cambridge Declaration calling for zero deaths, zero new infections, and zero suffering. "I think that the FAST method and what we have discussed today is a way forward for achieving zero TB deaths," Keshavjee said.

THE ROLE OF THE BRICS COUNTRIES

Continuing with the theme of the role of socioeconomic factors in TB, Keshavjee noted that the BRICS countries still have a great deal of poverty. Reflecting on the link between poverty and rates of TB, he cited the example of Brazil, where the number of people living in extreme poverty has fallen dramatically during the past 20 years. Over the same period, Brazil's TB rate has declined by 50 percent, while the global rate has declined by only 15 percent. "I'm not suggesting that we shift our focus away com-

pletely from biomedicine to the business of economic development," said Keshavjee. "[But] this shows us that if you have people coming out of poverty you probably get less disease, you're able to fight disease better, and you have better outcomes if you have disease. This should convince us that we have to think about having some component that invests in the social aspects of TB for our patients as an integral part of every program."

The BRICS countries could provide leadership for TB treatment and control, Keshavjee said, echoing comments made throughout the workshop. He reiterated the commitments made in the Delhi Ministerial Communiqué, in which the BRICS health ministers recognized that MDR TB is a major public health problem for their countries. The ministers resolved to

- collaborate and cooperate for the development of capacity and infrastructure;
- reduce the prevalence and incidence of TB through innovation in drugs/vaccines and diagnostics and the promotion of consortia of TB researchers; and
- collaborate on clinical trials of drugs and vaccines, strengthening access to affordable medicines and the delivery of high-quality care.

The ministers also recognized the need to cooperate in adopting and improving systems for

- notification of TB patients;
- availability of anti-TB drugs at treatment facilities through improved supplier performance; and
- procurement and the logistics and management of HIV-associated TB in the primary health care system.

In conclusion, Keshavjee said:

> Everything we have been talking about they seem to want to do. Is there some scenario where we can imagine that the BRICS countries will take a leadership role moving forward? The BRICS countries have a high proportion of the global burden of disease. They also have growing economies. . . . These countries are well poised to commit to scaling up the treatment of MDR TB and the treatment of regular TB. . . . We need to think big coming out of this meeting about what we expect from our host and the other BRICS countries.

13

Creating an Evidence-Based Blueprint for Action

In the penultimate session of the workshop, several speakers, including session chairs, individually identified potential options for moving forward that emerged from the presentations and discussions, highlighting those that, in the individual speakers' views, are supported by evidence. This chapter provides an integrated summary of the remarks made during that session, organized thematically into four broad areas of interest: pediatric DR TB, genomic tools and diagnostics, transmission, and drug supply and access. Speakers also addressed a fifth, cross-cutting theme: that of the opportunity to improve global awareness and the visibility of DR TB. Note that this summary should not be construed as reflecting consensus or endorsement by the workshop participants, the planning committee, the Forum, or the National Academies.

ADDRESSING DRUG-RESISTANT TB IN CHILDREN[1]

Children have a high risk of severe disease and death when infected with *M.tb*., said both Mercedes C. Becerra, Harvard Medical School, and Qian Gao, Professor, Shanghai Medical College, Fudan University, China. Bacteriologic confirmation of TB disease in children also is very difficult, even with invasive procedures. For that reason, the decision to treat a case of TB disease in a child as drug resistant often relies on a combination of

[1] This section is based on presentation by by Mercedes C. Becerra, Associate Professor, Department of Global Health and Social Medicine, Harvard Medical School, and Qian Gao, Professor, Shanghai Medical College, Fudan University, China.

clinical evaluation and known exposure to a source patient with DR TB. Cure rates in children exceeding 80 percent have been documented around the world using regimens that are tailored to the child's susceptibility profile or to that of the source case, even in children who are coinfected with HIV.

Becerra and Gao listed several potential action items and resource needs that could help expose and address the "silent epidemic" of DR TB in children:

- Children with DR TB can be a key indicator to help guide a large-scale policy response. The identification of children with DR TB allows for the monitoring of gaps, needed drugs, and whether programs are accessing the support they need to deliver care to children.
- Adoption of 1-year targets for the treatment of DR TB in children at the global, country, and institutional levels could help improve treatment rates. Targets could be defined either in terms of absolute numbers or as a percentage of the treatment for drug-resistant patients. To complement these efforts, institutions and countries could improve reporting of how many children are being treated and how many are waiting for treatment.
- Tests diagnosing TB and identifying drug resistance that perform well in children need to be developed.
- Treatment regimens need to be optimized for pediatric disease. This can be done using both prospective and retrospective approaches. A wealth of clinical information is available from around the world, including information on children, but the right partners and analytic tools are needed to deal with retrospective data. Funding for this research also is needed.
- Drugs in child-friendly formulations are needed. In addition, more needs to be known about the pharmacokinetics and pharmacodynamics of old and new drugs to optimize dosing in children.
- Ongoing exchange needs to be supported and promoted among clinicians and researchers to share best practices and accelerate learning in real time; exchange needs to occur across countries and needs to overcome language barriers.

ADOPTING GENOMIC TOOLS TO MAP THE EPIDEMIC OF DRUG-RESISTANT TB AND ADDRESS DIAGNOSTIC CHALLENGES[2]

Whole-genome sequencing could reveal drug-resistant strains, compensatory mutations, highly transmissible strains, and other characteristics of the pathogen, said Sven Hoffner, WHO Supranational Tuberculosis Reference Laboratory and Swedish Institute for Communicable Disease Control; and Yanlin Zhao, China CDC. Molecular epidemiology could trace outbreaks, risk groups, and risk settings and thus contribute to infection control efforts. In addition, epigenetic studies could increase understanding of host–pathogen interactions.

Hoffner and Yanlin Zhao proposed the following areas of need for further consideration:

- New diagnostics need to be scaled up from pilot sites to the national level.
- Studies using molecular diagnostic tests need to be conducted to understand the mechanism of resistance and to develop reliable phenotypic DST.
- Development of test algorithms for the evaluation of new tests could ensure that poor-quality tests are avoided and reliable results are obtained.
- Trial sites need to be staffed with experienced and knowledgeable investigators, particularly in the BRICS countries.
- Plans for national laboratory networks need to take into account new diagnostic tests, human resource development, and infection control needs.
- The roles of microscopy, microbial culture, and molecular testing should be evaluated and optimized to allow for sensitive, specific, and timely detection of MDR and XDR TB.
- A central body should be in charge of the entire laboratory network, including private laboratories. Basic quality criteria and a licensing system should be established to ensure high-quality service throughout the national laboratory networks, especially in the more peripheral laboratories.
- A laboratory information system and a database of genetic analysis and clinical data should be developed to ensure effective data handling, improve test quality, and enhance timely reporting.

[2] This section is based on the presentations by Sven Hoffner, Director, WHO Supranational Tuberculosis Reference Laboratory; and Department for Preparedness, Swedish Institute for Communicable Disease Control; and Yanlin Zhao, Vice Director, National Center for Disease Control and Prevention; and Director, National Tuberculosis Reference Laboratory, China CDC.

- Resources are needed to implement more rapid tests as soon and as widely as possible.

BLOCKING TRANSMISSION OF DRUG-RESISTANT TB[3]

Although TB is an airborne disease, not enough attention has been given to transmission control, said Edward A. Nardell, Brigham and Women's Hospital, Harvard Medical School; and Lixin Zhang, Deputy Director, Chinese Academy of Sciences Key Laboratory of Pathogenic Microbiology and Immunology; and Inaugural Director, Drug Discovery Center for Tuberculosis, IMCAS. Community-based treatment is at least as effective as hospital-based treatment and, importantly, is more likely to reduce transmission. Patients who are on effective therapy quickly become noninfectious, even if they remain smear positive.

Nardell and Lixin Zhang made the following points:

- Hospitals and clinics need to uncover the prevalence in their respective settings of unrecognized TB or unrecognized drug resistance, as these cases are a key source of transmission.
- Routine active case finding through cough surveillance of all hospital admissions and other means is an effective approach to transmission control, especially if combined with molecular rapid testing for TB and for MDR TB. To stem transmission, cough detection needs to progress to diagnosis and effective therapy within a matter of days, not months. Individual tests, which could overcome the difficulty of obtaining sputum samples, are a promising new screening technology on which several companies are working.
- Environmental control and respiratory protection remain important until effective treatment starts and, on an ongoing basis, for patients with XDR TB. Architectural and engineering capacity to implement these controls and protections needs to be improved.
- The incidence of TB and of MDR TB among health care workers needs to be monitored at the institutional level, and efforts to improve reporting are needed as well. Health care workers need comprehensive employee health programs, including preventive therapy for TB.

[3] This section is based on the presentations by Edward A. Nardell, Associate Professor, Division of Global Health, Brigham and Women's Hospital, Harvard Medical School; and Lixin Zhang, Deputy Director, Chinese Academy of Sciences Key Laboratory of Pathogenic Microbiology and Immunology; and Inaugural Director, Drug Discovery Center for Tuberculosis, IMCAS.

- Transmission control, including the development of new technologies and approaches, is as important a focus of attention as new diagnostics and drugs.

REFORMING DRUG DISTRIBUTION AND ASSURING DRUG QUALITY[4]

The drug development pipeline at the preclinical development stages is almost completely empty. "You cannot address an infectious disease that generates resistance without having an ongoing pipeline," said Barry R. Bloom, Harvard School of Public Health. In addition, new and more capable molecular diagnostics could greatly speed up diagnosis, which would be "a tremendous stride forward." Bloom noted that these principles reinforce the need for basic, developmental, and operational research.

Bloom offered the following proposals for next steps:

- The most limiting factor in the supply of drugs is a lack of information. What will be the need? How many doses will be bought? How many doses will be used? How much should be produced? What are the lead times for producers? According to Bloom, TB forecasting needs to be linked with forecasting for other diseases and drugs, with input from experts in both the public and private sectors.
- The countries that are sources of the production of drugs and thus must try to forecast future needs will need to work with regulatory authorities to make improvements in the later stages of the drug supply chain—allowing quicker production and dissemination of quality drugs so they reach patients. This cooperation between countries and regulatory authorities would also ensure greater supplies, more producers, more competition, and lower prices.
- Better provision of anti-TB drugs also will require more funding than is available today. Increased funding through the Global Fund or other international mechanisms could help guarantee markets, provide continuity to producers, inform better forecasts, and increase the visibility of TB. However, many of the HBCs have "graduated" from the Global Fund grants, potentially lengthening the impact of this intervention.
- An up-front pooled capital fund would reduce the need for each country to negotiate separately with a large number of producers.

[4] This section is based on the presentation by Barry R. Bloom, Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, Department of Immunology and Infectious Diseases, Harvard School of Public Health.

Even expensive drugs can be cost-effective if they keep the MDR/XDR disease from spreading. Moreover, up-front payments and guarantees could bring prices down.

- Drugs that are prequalified by WHO or stringent regional regulatory authorities should not have to go through an extended period of regulatory review within individual countries. Regional regulatory agreements can avoid the need for repeated validations by agencies in each country.
- Adequate funding needs to be applied for training in how to run supply chains, assess and assure quality, and comply with regulations; such training would be useful not only for TB drugs but for other drugs as well.
- Improved organization and leadership are needed to strengthen the supply of drugs for DR TB. Public–private partnerships could be a way to make expertise in the private sector available to the public sector.

Bloom also observed that successful community-based care of MDR TB patients, such as that implemented in South Africa and elsewhere, is very promising and could be generalized to many other countries.

INCREASING THE VISIBILITY OF DRUG-RESISTANT TB

Panelists also addressed the need for improved global awareness and visibility of the problem of DR TB. Millennium Development Goal 6 calls for combating HIV/AIDS, malaria, and "other diseases." As Bloom said of TB, "When a disease which is this fatal and this threatening to the world is termed an 'other' disease . . . we have done a poor job of getting the message through."

Information about DR TB needs to be simplified so that political leaders and members of the public can understand and act on it, said Bloom. As an example, he proposed a "marketing" strategy, proclaiming, "With the appropriate funds, leadership, and organization, we can save *X* number of lives every year and prevent *Y* number of lives from being infected with drug-resistant TB."

Gao made a similar point in his remarks, noting that better treatment will require greater societal involvement, which in turn will require that MDR TB be acknowledged as a serious disease. TB and MDR TB are as much a social as a medical problem. "Without society paying attention to MDR TB, we cannot solve this problem," he said. In that respect, countries could learn from the response to the HIV epidemic, whereby recognition of the magnitude of the problem led to a greater response than has been the case with DR TB.

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Appendix A

Workshop Agenda

THE GLOBAL CRISIS OF DRUG-RESISTANT TUBERCULOSIS AND THE LEADERSHIP OF THE BRICS COUNTRIES: CHALLENGES AND OPPORTUNITIES

Wednesday–Friday, January 16–18, 2013
Beijing, China

The increasing burden of drug-resistant tuberculosis 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 3-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), and the Institute of Microbiology of the Chinese Academy of Sciences (CAS). Following an inaugural meeting in Washington, DC, in 2008, this workshop in Beijing is the fourth in a series of international workshops convened by the U.S. IOM. The objective of the workshop series is to realistically assess the impact of and challenges resulting from drug-resistant TB globally and in the four countries with the most people affected (China, India, Russia, and South Africa). A public workshop was also convened in July/August 2012 in Washington, DC, to identify opportunities to improve the global supply chain for second-line TB drugs. Specifically, the goals of the workshop series include

- Consider a wide spectrum of issues pertaining to the science and policy around drug-resistant tuberculosis—from biology, epide-

miology, 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 global "blueprint for action."

- Present promising new research, and also to identify specific gaps in knowledge and consider potential needs for additional research, funding, and international attention.

The workshop series has been hosted over a period of several years, creating a venue and body of knowledge that explicitly considers and addresses developments over a period of time, 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 results in a U.S. National Academies publication summarizing the workshop presentations and discussions.

This workshop in Beijing will address the current status of drug-resistant tuberculosis globally, and in China, and consider lessons learned from the other three high burden countries; highlight global 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. The workshop will consider urgent themes relating to the problem of multidrug-resistant (MDR) TB, extensively drug resistant (XDR) TB, and emergent TB strains that are potentially untreatable with drugs available and will consider the critical leadership role of the BRICS countries in addressing the threats and opportunities in drug-resistant TB.

THE GLOBAL CRISIS OF DRUG-RESISTANT TUBERCULOSIS AND THE LEADERSHIP OF THE BRICS COUNTRIES: CHALLENGES AND OPPORTUNITIES

Wednesday, January 16, 2013
Beijing, China

DAY 1

7:00 a.m. Registration

8:30 a.m. ***Welcome and Introductory Remarks***
(Moderator: LIXIN ZHANG)

YAPING ZHANG
Vice President
Chinese Academy of Sciences

9:00 a.m. Group Photo

9:15 a.m. ***Global Burden, Themes from Institute of Medicine Workshops in Other BRICS Countries, and Workshop Goals***

GAIL CASSELL
Chair, IOM Planning Committee
Harvard Medical School
Infectious Disease Research Institute

GEORGE FU GAO
Vice Director General
Chinese Center for Disease Control and Prevention
Beijing Institute of Biological Sciences, CAS

9:45 a.m. **Opening Keynote Address**

Twenty-Five Years After the First Major MDR TB Outbreak: Is It Time for a New Strategy?

PAUL FARMER
Chair, Department of Global Health and Social Medicine
Harvard Medical School

10:15 a.m. BREAK

10:45 a.m. ***Panel Discussion: Challenges and Opportunities for the BRICS Country Leadership***

The BRICS countries, represented by the Ministers of Health of the Federative Republic of Brazil, the Russian Federation, India, People's Republic of China, and Republic of South Africa, met in New Delhi on 11 January 2013 at the Second BRICS Health Ministers' Meeting. The Ministers recognized that multidrug-resistant tuberculosis is a major public health problem for the BRICS countries due to its high prevalence and incidence mostly on the marginalized and vulnerable sections of society. They resolved to

- collaborate and cooperate for development of capacity and infrastructure to reduce the prevalence and incidence of tuberculosis through innovation for new drugs/vaccines, diagnostics; and
- promotion of consortia of tuberculosis researchers to collaborate on clinical trials of drugs and vaccines;
- strengthening access to affordable medicines and delivery of quality care.

The Ministers also recognized the need to cooperate for adopting and improving systems for notification of tuberculosis patients, availability of anti-tuberculosis drugs at facilities by improving supplier performance, and procurement systems and logistics and management of HIV-associated tuberculosis in the primary health care system.

The Ministers also recognized the importance and need of technology transfer as a means to empower developing countries. In this context, they underlined the important role of generic medicines in the realization of the right to health. The Ministers renewed their commitment to strengthening international cooperation in health, in particular south–south cooperation, with a view to supporting efforts in developing countries to promote health for all and resolve to establish the BRICS network of technological cooperation. (Delhi Communiqué, January 12, 2013, http://pib.nic.in/newsite/erelease.aspx?relid=91533)

Rifat Atun
Professor of International Health Management
Imperial College
London

Kristina Wallengren
Clinical Advisor
KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH)

Salmaan Keshavjee
Associate Professor, Department of Global Health and Social Medicine
Harvard Medical School

GRIGORY VOLCHENKOV
Head Doctor
Vladimir Oblast TB Dispensary
Center of Excellence for TB Infection Control

YANLIN ZHAO
Vice Director, National Center for Disease Control and Prevention
Director, National Tuberculosis Reference Laboratory
Chinese Center for Disease Control and Prevention

11:30 a.m. Discussion with speakers and audience

Moderators:

GAIL CASSELL
Harvard Medical School
Infectious Disease Research Institute

YANLIN ZHAO
Vice Director, National Center for Disease Control and Prevention
Director, National Tuberculosis Reference Laboratory
Chinese Center for Disease Control and Prevention

12:00 p.m. LUNCH

SESSION I: DRUG-RESISTANT TB IN CHINA

Session Objectives:

- Describe the health care delivery system in China and recent surveillance results of drug-resistant TB in China. Identify where data are missing and are most needed.
- Discuss the burden of drug-resistant TB in China from the perspective of clinicians and health care providers.
- Present data on the burden of drug-resistant TB in vulnerable populations such as domestic migrant workers and individuals with comorbidities, including HIV and diabetes.
- Present international perspectives on the impact of health delivery systems on DR TB control and care.

Session Chairs:

- China co-chair: FABIO SCANO, World Health Organization
- U.S. co-chair: PAUL FARMER, Harvard Medical School

1:30 p.m. ***Overview of the Health Care Delivery System and Programmatic Management of MDR TB in China***

MINGTING CHEN
Vice Director/Researcher
National Center for Tuberculosis Control and Prevention
Chinese Center for Disease Control and Prevention

2:00 p.m. ***2007 National Survey of Drug Resistance in China***

YANLIN ZHAO
Vice Director, National Center for Disease Control and Prevention
Director, National Tuberculosis Reference Laboratory
Chinese Center for Disease Control and Prevention

2:30 p.m. ***Panel Discussion: Perspectives from Public Health and Hospital Systems in China***
[20 min. each speaker]

Clinical Diagnosis and Treatment of Drug-Resistant TB
WENHONG ZHANG
Huashan Hospital of Fudan University, Shanghai, China

M/XDR TB Chemotherapy in China
SHOU-YONG TAN
Guangzhou Chest Hospital

3:10 p.m. BREAK

3:30 p.m. ***Panel Discussion: Treating Drug-Resistant TB in Vulnerable Populations in China***
[20 min. each speaker]

Drug-Resistant TB and HIV in China
LIU FEIYING
Guangxi Center for Disease Control and Prevention, China

Drug-Resistant TB and Diabetes in China
CHU NAIHUI
(Oral presentation by Duan Hongfei)
Beijing Chest Hospital

4:10 p.m. Discussion with speakers and audience

4:30 p.m. ***Panel Discussion: Impact of Health Care Delivery Systems on DR TB***
[20 min. each speaker]

Peru, Russia, and Lesotho
SALMAAN KESHAVJEE
Associate Professor
Department of Global Health and Social Medicine
Harvard Medical School

Community-Based Care in South Africa
KRISTINA WALLENGREN
Clinical Advisor
KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH)

Direct Collaboration and "South-to-South Transfer" in Cambodia and Ethiopia
ANNE GOLDFELD
Harvard Medical School/Global Health Committee

5:30 p.m. Discussion with speakers and audience

6:00 p.m. Closing remarks and adjourn day 1

THE GLOBAL CRISIS OF DRUG-RESISTANT TUBERCULOSIS AND THE LEADERSHIP OF THE BRICS COUNTRIES: CHALLENGES AND OPPORTUNITIES

Thursday, January 17, 2013
Beijing, China

DAY 2

SESSION II: TRANSMISSION AND INFECTION CONTROL: EPIDEMIOLOGICAL AND GENOTYPIC EVIDENCE AND CONSEQUENCES

Session Objectives:

- Provide an overview of the epidemiological, phenotypic, and genotypic evidence for primary transmission of drug-resistant TB.
- Discuss the consequences of transmission of drug-resistant TB in communities and hospitals.
- Consider the scientific evidence for active case finding, rapid diagnosis, and treatment based on drug-susceptibility testing (DST) to stop transmission.
- Discuss the role of infection control in China today and consider infection control policies and practices in other countries with a high prevalence of drug-resistant TB.
- Describe drug-resistant TB risk factors (e.g., inadequate treatment, losing patients during follow-up, drug shortages, exposure to drug-resistant TB due to inadequate infection control) and provide in-country perspectives of the issues and current strategies for prevention and control.

Session Chairs:

- China co-chair: WENHONG ZHANG, Huashan Hospital of Fudan University
- U.S. co-chair: EDWARD NARDELL, Harvard School of Public Health

8:00 a.m. ***Global Perspective on Transmission: Value in Genotype Mapping of Disease Transmission Dynamics***

NEEL GANDHI
Associate Professor
Department of Epidemiology
Rollins School of Public Health
Emory University

8:30 a.m. ***Current Status of Infection Control in China: Different Perspectives***
[20 min. each speaker]

Hospital System Perspective
LIANG LI
Clinical Center for Tuberculosis, China CDC

Public Health Systems
GUANGXUE HE
Chinese Center for Disease Control and Prevention

Infection Control Challenges
CAROL RAO
U.S. Centers for Disease Control and Prevention

9:30 a.m. Discussion with speakers, panelists and audience

10:00 a.m. BREAK

10:20 a.m. ***Perspectives on Infection Control in Other Countries***
[20 min. each speaker]

South Africa
CARRIE TUDOR
Fogarty Global Health Postdoctoral Fellow
Johns Hopkins School of Nursing

Institutional Infection Control in Russia
GRIGORY VOLCHENKOV
Head Doctor
Vladimir Oblast TB Dispensary
Center of Excellence for TB Infection Control

11:00 a.m. ***Redesign of Health Care Facilities, Active Case Finding, Rapid Diagnosis, and Effective Treatment Based on DST to Stop Transmission in Institutional and Community Settings***

EDWARD NARDELL
Associate Professor
Departments of Environmental Health and Immunology and Infectious Diseases, Harvard School of Public Health

11:30 a.m. Discussion with speakers and audience

11:45 a.m. LUNCH

SESSION III: RAPID DIAGNOSTIC TECHNOLOGY: CURRENT STATUS AND LIMITATIONS

Session Objectives:

- Provide an overview of the methods of DST used globally and the advantages and disadvantages of different tests.
- Discuss the current use of diagnostic tests for drug-susceptible and drug-resistant TB in China and identify the barriers to rapid diagnosis and management of patients. Consider challenges in diagnosing TB and drug-resistant TB vs. nontuberculous mycobacteria (NTM). Provide a laboratory- and hospital-based perspective on DST.
- Discuss work from other countries in implementing programs for rapid diagnosis of drug-resistant TB and consider the populations in which various DSTs work best.

Session Chairs:

- China co-chair: JACK ZHANG, PATH
- U.S. co-chair: JEAN-LUC BERLAND, Fondation Mérieux

1:00 p.m. ***DST in Detecting DR TB, Overview of Other Technologies, and Rollout of GeneXpert in South Africa: What Are the Gaps?***

MARK NICOL
Division of Medical Microbiology and Institute for Infectious Diseases and Molecular Medicine
University of Cape Town and National Health Laboratory Service
South Africa

1:30 p.m. ***Panel Discussion: Perspectives on Drug-Resistant TB Diagnostic Technologies in Use in China***
[15 min. each speaker]

SAT-TB Assay
JIN CHEN
Shanghai Pulmonary Disease Hospital

GeneXpert
YAO-JU TAN
Guangzhou Chest Hospital

GenoType MTBDRplus
WEI GE
Shandong Chest Hospital

Line Probe Assay (LPA)
HAIRONG HUANG
Beijing Chest Hospital

Cross Priming Amplification (CPA)
PANG YU
Chinese Center for Disease Control and Prevention

2:45 p.m. ***Genetic Diversity of DR TB: Implication for Future Diagnostics***

MEGAN MURRAY
Professor
Department of Global Health and Social Medicine
Harvard Medical School

3:15 p.m. Discussion with speakers and audience

3:30 p.m. BREAK

SESSION IV: ADDRESSING DIAGNOSIS AND TREATMENT ACROSS THE SPECTRUM OF DRUG RESISTANCE

Session Objectives:

- Describe the prevalence of MDR, pre-XDR, XDR, and untreatable TB in key countries.
- Consider the diagnosis and treatment challenges associated with MDR, pre-XDR, and XDR TB. How can a TB program effectively meet the needs of patients?

Session Chairs:

- China co-chair: JIN LIANG JU, Shanghai Pulmonary Disease Hospital
- U.S. co-chair: NEEL GANDHI, Emory University

3:45 p.m. ***MDR and XDR TB***

Clinical Perspective
RICHARD CHAISSON
Johns Hopkins University

4:05 p.m. ***Panel Discussion: Treating the Spectrum of Drug Resistance in China***
[20 min. each speaker]

New Diagnostic Marker Screening in TB Meningitis
XIAOYOU CHEN
Tuberculosis Department, Beijing Chest Hospital
Beijing Tuberculosis & Thoracic Tumor Research Institute

Surgical Treatment of M/XDR TB
XIAO NING
Beijing Chest Hospital, Capital Medical University

4:45 p.m. *The Need for a Paradigm Shift in Treatment of the Spectrum of Drug Resistant TB*
MARKUS MAEURER
Professor and Head, Therapeutic Immunology Division
Karolinska Institute

5:15 p.m. ***MDR, XDR, and Untreatable TB from a Laboratory Perspective***
[20 min. each speaker]

MARTIE VAN DER WALT
Interim Director, TB Epidemiology and Intervention Research Unit
South African Medical Research Council

SVEN HOFFNER
Director, WHO Supranational TB Reference Laboratory
Associate Professor, Department for Preparedness
Swedish Institute for Communicable Disease Control

5:55 p.m. ***Totally Drug-Resistant TB in India: Lessons and Opportunities from a Clinical Perspective***

ZARIR UDWADIA
Consultant Chest Physician
Hinduja Hospital
Mumbai, India

6:25 p.m. Discussion with speakers, panelists, and audience

7:15 p.m. Closing remarks and adjourn day 2

THE GLOBAL CRISIS OF DRUG-RESISTANT TUBERCULOSIS AND THE LEADERSHIP OF THE BRICS COUNTRIES: CHALLENGES AND OPPORTUNITIES

Friday, January 18, 2013
Beijing, China

DAY 3

SESSION V: DRUG-RESISTANT TB IN PEDIATRIC POPULATIONS

Session Objectives:

- Review the global burden and transmission of pediatric DR TB.
- Discuss challenges in diagnosis and treatment of DR TB in children.

Session Chairs:

- China co-chair: QIAN GAO, Fudan University, China
- U.S. co-chair: MERCEDES BECERRA, Harvard Medical School

8:00 a.m. ***Children as Sentinels for Transmission and Policy Response***

MERCEDES BECERRA
Associate Professor
Department of Global Health and Social Medicine
Harvard Medical School

8:30 a.m. ***Pediatric Drug-Resistant TB in China***

TAO LI
Shanghai Public Health Clinical Center

8:50 a.m. ***Drug-Resistant TB in Meningitis***

SHUNYING ZHAO
(Oral presentation by Huimin Li)
Beijing Children's Hospital

9:10 a.m. ***Status of Pediatric MDR/XDR TB in the Russian Federation and Other Former Soviet Union Countries: Managing Pediatric Drug-Resistant TB in a Setting with Separate Medical Structures for Adults and Children***

VALENTINA AKSENOVA
(Oral presentation by Rita Guenther)
Head, Childhood and Adolescent Tuberculosis Department
Research Institute of Phthisiopulmonology
First Moscow Sechenov State Medical University
Chief Pediatric Phthisiologist, Ministry of Health, Russian Federation

9:30 a.m. Discussion with speakers and audience

9:45 a.m. BREAK

SESSION VI: LOOKING FORWARD: DEVELOPING AND STRENGTHENING THE DRUG SUPPLY CHAIN FOR DRUG-RESISTANT TB

Session Objectives:

- Consider to what extent and in what ways current supply chain mechanisms are or are not effectively accomplishing what is needed, in China and beyond, including consideration of bottlenecks.
- Consider the current allocation of responsibilities and roles of the private (including industry and not-for-profit public health organizations) and public sectors, and examination of opportunities for enhancing and optimizing collaboration.
- Identify potential innovative solutions to the supply chain problem.

Session Chairs:

- China co-chair: WENHONG ZHANG, Huashan Hospital, Fudan University
- U.S. co-chair: BARRY BLOOM, Harvard School of Public Health

10:00 a.m. ***Barriers, Challenges, Needs, and Potential Solutions for the SLD Supply Chain***

BARRY BLOOM
Co-chair, IOM workshop, Developing and Strengthening the Global Supply Chain for Second-Line Drugs for MDR TB
Distinguished Service Professor
Department of Immunology and Infectious Diseases
Harvard University
Dean of the Harvard School of Public Health (former)

10:20 a.m. ***Panel: Different Perspectives on the Global Supply Chain***

RIFAT ATUN
Professor of International Health Management
Imperial College
London

DAN COLLINS
Corporate Affairs
Eli Lilly and Company

MINGTING CHEN
Chinese Center for Disease Control and Prevention

DALE NORDENBERG
Chief Executive Officer
Novasano Health and Science

OSKAR SLOTBOOM
Head, Vaccine and Infectious Diseases
Xian Janssen Pharmaceutical Ltd., Johnson & Johnson

11:30 a.m. Discussion with speakers and audience

11:45 a.m. LUNCH

SESSION VII: LOOKING FORWARD: EMBRACING A NEW VISION FOR RESEARCH

Session Objective:

- Review the state of the art in TB research and identify opportunities to apply new research tools to the problem of DR TB.

Session Chairs:

- China co-chair: MIN FANG, Institute of Microbiology, Chinese Academy of Sciences
- U.S. co-chair: ANNE GOLDFELD, Harvard Medical School/Global Health Committee

1:00 p.m. ***The Need for a Paradigm Shift in TB Research: Synergy of Discovery and Delivery of Care***

ANNE GOLDFELD
Harvard Medical School/Global Health Committee

1:30 p.m. ***New Tools to Facilitate TB Research***
[10 min. each speaker]

NIH Global TB Research Resources
MARIA GIOVANNI
Director, Office of Genomics and Advanced Technologies
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
U.S. National Institutes of Health

TBResist: A Global Consortium for Whole Genome Sequencing of Drug-Resistant TB
GAIL CASSELL
Harvard Medical School
Infectious Disease Research Institute

Chemogenomics
PATRICK TAO LI
BGI (formerly Beijing Genomics Institute)

Meta-Analysis
KATHRYN DERIEMER
University of California, Davis

2:10 p.m. Discussion with speakers, panelists, and audience

SESSION VIII: CREATING AN EVIDENCE-BASED BLUEPRINT FOR ACTION: IDENTIFICATION OF FOUR STEPS

Session Objective:

- Present highlights from the workshop and identify a blueprint for action based on discussions from the previous 2.5 days.

Session Chairs:

- China co-chair: YANLIN ZHAO, Chinese Center for Disease Control and Prevention
- U.S. co-chair: GAIL CASSELL, Harvard Medical School and Infectious Disease Research Institute

2:30 p.m. ***Action #1: Expose and Address the Silent Epidemic of DR TB in Children: Evidence Challenges and Mobilization of a Global Network***

MERCEDES BECERRA
Associate Professor
Department of Global Health and Social Medicine
Harvard Medical School

QIAN GAO
Fudan University, Shanghai

2:45 p.m. ***Action #2: Adopt Genomic Tools to Map the Epidemic of Drug-Resistant TB and Address Diagnostic Challenges***

SVEN HOFFNER
Director, WHO Supranational TB Reference Laboratory
Associate Professor, Department for Preparedness
Swedish Institute for Communicable Disease Control

YANLIN ZHAO
Vice Director, National Center for Disease Control and Prevention
Director, National Tuberculosis Reference Laboratory
Chinese Center for Disease Control and Prevention

3:00 p.m. ***Action #3: Block Transmission of Drug-Resistant TB***

EDWARD NARDELL
Associate Professor
Departments of Environmental Health and Immunology and Infectious Diseases
Harvard School of Public Health

LIXIN ZHANG
Deputy Director, CAS Key Laboratory of Pathogenic Microbiology & Immunology
Inaugural Director of Drug Discovery Center for Tuberculosis
Institute of Microbiology, Chinese Academy of Sciences

3:15 p.m. ***Action #4: Revolutionize Drug Distribution, Guarantee Drug Quality, and Reform Regulatory Approval and Registration Policies***

BARRY BLOOM
Distinguished Service Professor
Department of Immunology and Infectious Diseases
Harvard University
Dean of the Harvard School of Public Health (former)

3:30 p.m. BREAK

SESSION IX: A BIOSOCIAL APPROACH: SCIENCE AND ECONOMIC INTERVENTION FOR DR TB CONTROL—BRICS AT THE FOREFRONT

Session Objective:

- Discuss the leading role of BRICS countries in the effort to combine science and evidence-based policies with economic interventions to combat DR TB.

Session Chairs:

- China co-chair: YANLIN ZHAO, Chinese Center for Disease Control and Prevention
- U.S. co-chair: RIFAT ATUN, Professor of International Health Management, Imperial College London

3:45 p.m. ***What Will Be Required for Zero Deaths from Drug-Resistant TB?***

SALMAAN KESHAVJEE
Associate Professor
Department of Global Health and Social Medicine
Harvard Medical School

4:15 p.m. ***Reflections from BRICS Countries: What Are the Next Steps?***

RIFAT ATUN
Professor of International Health Management
Imperial College
London

PAUL FARMER
Chair, Department of Global Health and Social Medicine
Harvard Medical School

KRISTINA WALLENGREN
Clinical Advisor
KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH)

GRIGORY VOLCHENKOV
Head Doctor
Vladimir Oblast TB Dispensary
Center of Excellence for TB Infection Control

YANLIN ZHAO
Vice Director, National Center for Disease Control and Prevention
Director, National Tuberculosis Reference Laboratory
Chinese Center for Disease Control and Prevention

5:15 p.m. Discussion with speakers and audience

6:00 p.m. ***Reflections on the New Delhi Communiqué***

JARBAS BARBOSA (by teleconference)
Vice-Minister of Health
Federative Republic of Brazil

6:15 p.m. Adjourn day 3 and workshop

7:00 p.m. BANQUET

Appendix B

Participant Biographies

Valentina Aksenova, M.D., is Head of the Children and Adolescents Department, Research Institute of Physiopulmonology of the First Sechenov Moscow State Medical University, and Chief Freelance Expert Pediatrician-Physiologist of the Russian Health Ministry. Dr. Aksenova graduated from the 2nd Pirogov Moscow Medical Institute as a pediatrician. Since 1981, she has been working in the Research Institute of Physiopulmonology, Children and Adolescents Department, starting as junior scientific worker and now working as Head of the Department. Since 1991, she has been the Chief Freelance Expert Pediatrician-Physiologist of the Russian Health Ministry and the Head of the Health Ministry Republic Centre for BCG Complications. Since 1998, she has been Professor of Physiopulmonology and Chair of the Postgraduate Education Faculty of the 1st Sechenov Moscow State Medical University. Since 2001, she has been a member of the WHO Eastern Europe Working Group for Childhood Tuberculosis. Dr. Aksenova is also a member of the Russian Society of Physiologists, the World Association of Pediatricians, and The Union. Her areas of research interest include issues of physiopulmonology and pulmonology in children and adolescents, pediatrics, and organization of health care in the continents. She has authored more than 300 scientific publications; 25 Ph.D. and 4 M.D. theses were completed under her guidance. The Russian Ministry of Health awarded her the Medal of Merit for domestic health care.

Rifat Atun, M.B.B.S., M.B.A., FRCGP, FFPH, FRCP, is Professor of International Health Management, Imperial College Business School and Faculty of Medicine, Imperial College London. He heads the Health Management

Group at Imperial College Business School. Between 2008 and 2012, he was a member of the Executive Management Team at the Global Fund to Fight AIDS, Tuberculosis, and Malaria in Switzerland as the Director of Strategy, Performance and Evaluation Cluster. Since 2009, he has been the Chair of the Stop TB Partnership Coordinating Board. Dr. Atun has worked globally with the UK Department for International Development (DFID), the DFID Resource Centre for Health Systems, the World Bank, WHO, and other international health agencies to design, implement, and evaluate health systems reforms and communicable and noncommunicable disease programs. His research focuses on innovation in health systems. Dr. Atun was a member of the Strategic Technical Advisory Group of WHO for Tuberculosis and the Advisory Committee for the WHO Research Centre for Health Development in Japan. He is a member of the Scientific Advisory Board for PEPFAR, the Global Health Group at the UK Medical Research Council, and the Global Task Force for Expanding Cancer Care and Control in Developing Countries. He has published extensively on health systems, communicable disease control, and innovation in health and biopharmaceutical sectors. Dr. Atun studied medicine at the University of London as a Commonwealth Scholar and completed his postgraduate medical studies and master's degree in business administration at University of London and Imperial College London. He is a Fellow of the Faculty of Public Health of the Royal College of Physicians (UK), a Fellow of the Royal College of General Practitioners (UK), and a Fellow of the Royal College of Physicians (UK).

Mercedes C. Becerra, Sc.D., is Associate Professor in the Department of Global Health and Social Medicine at Harvard Medical School. She is a graduate of Harvard College (A.B., history) and earned an Sc.D. in epidemiology at the Harvard School of Public Health. Her research focuses on the treatment of TB and the TB burden in patient households. Dr. Becerra is the principal investigator of a large ongoing study of the epidemiology of DR TB in Peru, supported by grants from NIAID. She is also the recipient of a Charles H. Hood Foundation Child Health Research Award and a career development award from the National Heart, Lung, and Blood Institute. Dr. Becerra serves as a senior TB specialist with Partners In Health, an international nonprofit organization that provides direct health care services and advocates on behalf of those who are sick and living in poverty. She is co-founder of the Sentinel Project on Pediatric Drug-Resistant Tuberculosis, a global coalition of researchers, caregivers, and advocates seeking to end child deaths from this curable and preventable disease.

Jean-Luc Berland, M.Sc., is Assistant Scientist, Fondation Mérieux–Laboratoires des Pathogènes Emergents. Mr. Berland is interested in diag-

nostics of infectious disease. After receiving a master's degree in biochemistry from the Lyon 1 University, he joined the R&D Immunoassays Department of BioMérieux in 1995. He participated in the development of in vitro diagnostic reagents for the detection of various pathogens, including respiratory viruses and hepatitis C virus (HCV), as well as for characterization of the sera lipid particles containing HCV and development of tools for preclinical immune response monitoring of an HCV vaccine candidate concept. Since 2008, he has been responsible for a TB project in the Scientific Department of Fondation Mérieux. With its research programs, Fondation Mérieux pursues objectives such as developing diagnostic tools enabling improved epidemiological monitoring on a global scale, distributing these tools extensively, and promoting advanced research in developing countries. Fondation Mérieux has worked to create international scientific partnerships in countries in the field of TB, including HBCs. In partnership with local partners in several developing countries and through collaboration with international institutions, this program aims to implement and develop molecular tools and build capacities for the diagnosis of DR, MDR, and XDR TB.

Barry R. Bloom, Ph.D., D.Sc. (Hon.), is Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, Department of Immunology and Infectious Diseases, Harvard School of Public Health. Dr. Bloom is a graduate of Amherst College (B.S., 1958, and Hon. D.Sc., 1990) and Rockefeller University (Ph.D., 1963). He served as Dean of the Harvard School of Public Health from 1998 through 2008 and is a leading scientist in the areas of infectious diseases, vaccines, and global health. After more than 35 years as the principal investigator in a Harvard laboratory researching immune response to TB, he recently shut down his lab to concentrate on teaching and lecturing. He is a member of the NAS, the IOM, the American Association for the Advancement of Science, and the American Philosophical Society. While dean of the Harvard School of Public Health, Dr. Bloom served as secretary and treasurer for the Association of Schools of Public Health. Prior to joining Harvard, he served as chairman of the Department of Microbiology and Immunology at the Albert Einstein College of Medicine and as an investigator of the Howard Hughes Medical Institute, where he also served on the National Advisory Board. In 1978, he was a consultant to the White House on international health policy. He is a past president of the American Association of Immunologists and the Federation of American Societies for Experimental Biology. He received the first Bristol-Myers Squibb Award for Distinguished Research in Infectious Diseases, shared the Novartis Award in Immunology in 1998, and was the recipient of the Robert Koch Gold Medal for Lifetime Research in Infectious Diseases in 1999. Dr. Bloom has been extensively involved with WHO for more than 40 years. He is currently chair of the Technical

and Research Advisory Committee to the Global Programme on Malaria at WHO, has been a member of the WHO Advisory Committee on Health Research, chaired the WHO Committees on Leprosy Research and Tuberculosis Research, and chaired the Scientific and Technical Advisory Committee of the UN Development Programme/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. He is also a member of the Innovation Working Group under the UN Secretary General's Joint Effort to Improve the Health of Women and Children. Dr. Bloom serves on the Scientific Advisory Boards of the Earth Institute at Columbia University, the Doris Duke Charitable Foundation, City University of New York School of Public Health at Hunter College, and the Howard Hughes Medical Institute K-RITH. In addition, he is an Expert Advisory Group member of the Global Fund AMFm, and a Scientific Oversight Group member of the Institute for Health Metrics and Evaluation at the University of Washington, Seattle. He is a member of the Board of Trustees for the Tuberculosis Vaccine Institute and the first Chairman of the Board of Trustees and now Chairman Emeritus of the International Vaccine Institute. Most recently, he has joined the Advisory Board of the Fogarty International Center at NIH.

Gail H. Cassell, Ph.D., D.Sc. (Hon.), is Visiting Professor, Department of Global Health and Social Medicine, Harvard Medical School, and Vice President of TB Drug Development of the not-for-profit Infectious Disease Research Institute, Seattle, Washington. Dr. Cassell has recently retired as Vice President, Scientific Affairs, and Distinguished Eli Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company, Indianapolis, Indiana. In this capacity, among other things, she was responsible for initiating and leading the not-for-profit Eli Lilly TB Drug Discovery Initiative launched in 2007. In 2003, she was one of two individuals at Eli Lilly who initiated and developed the Eli Lilly Multidrug Resistant Tuberculosis Partnership. The partnership has resulted in company support to date of $135 million and is the largest philanthropic effort in Eli Lilly's 135-year history. The partnership now involves more than 20 partners, including WHO and U.S. CDC. She is the former Vice President of Infectious Diseases, Drug Discovery, and Clinical Development of Eli Lilly, where she led the programs of a hepatitis C protease inhibitor recently approved by FDA from the discovery phase to clinical candidate and the development of a new class of antibiotics from clinical development to product decision. Prior to moving to Eli Lilly in 1997, Dr. Cassell was the 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 which 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. She obtained her Ph.D. in microbiology from the University of Alabama at Birmingham and was selected as its 2003 Distinguished Alumnus. She is a past president of the American Society for Microbiology, the oldest and single largest life sciences organization, with a membership of more than 42,000 (more than 20 percent international members). She was named to the original Board of Scientific Councilors of the Center for Infectious Diseases, U.S. CDC, and served as Chair of the Board. She has served on the Advisory Board of the Director of NIH, the Director of U.S. CDC, and the Secretary of Health and Human Services Advisory Council of Public Health Preparedness, FDA's Science Board, the Advisory Committee to the Commissioner. Currently, she is a member of the NIH Science Management Board, the newly appointed NIH Board of Trustees, and the Advisory Council of the Fogarty International Center of NIH. Since 1996, she has been a member of the U.S.–Japan Cooperative Medical Science Program responsible for advising the respective governments on joint research agendas (U.S. State Department/Japan Ministry of Foreign Affairs). She was instrumental in the establishment of the U.S./Russia Cooperative Medical Sciences and Training Program under the Bilateral Presidential Commission in 2009, which represents a collaboration involving NIH, the NAS, the IOM, the Russian Academy of Sciences, and the Russian Academy of Medical Sciences. She has served on the editorial boards of several scientific journals and has authored more than 350 articles and book chapters. Dr. Cassell has received national and international awards for her research in infectious diseases, including two honorary degrees, the U.S. CDC Honor Award in Public Health for exceptional leadership and contributions in the development and implementation of U.S. CDC's Emerging Infectious Disease Plan 1997, a Citation from the FDA Commissioner for her role as chair of the review of science and technology at FDA and the report *FDA: Science and Mission at Risk 2008*, and the Emmy Klineberger-Nobel Award in 2008 from the International Organization for Mycoplasmology for outstanding and sustained research contributions to the field of mycoplasmology. She is a member of the IOM of the NAS and has recently completed a second 3-year term on the IOM Council (the governing board). She was elected in 2011 to membership on the U.S. Council of Foreign Relations and appointed by the Secretary of the Department of Health and Human Services as a member of the U.S. CDC Advisory Committee on Tuberculosis Elimination. Dr. Cassell has been intimately involved in the establishment of science policy and legislation related to biomedical research and public health. For 9 years she was Chair of the Public and Scientific Affairs Board of the American Society for Microbiology; she has served as an advisor on infectious diseases and indirect costs of research to the White House Office of Science and Technology Policy and has been an invited partici-

pant in numerous congressional hearings and briefings related to infectious diseases, antimicrobial resistance, and biomedical research. She has served two terms on the Liaison Committee on Medical Education, the accrediting body for U.S. medical schools, as well as on other national committees involved in establishing policies in training in the biomedical sciences. She is an emeritus member of the Board of Research!America and a former member and Chair of the Board of Directors of the Burroughs Wellcome Fund. She has recently completed terms on the Leadership Council of the School of Public Health of Harvard University, the Executive Committee of Columbia University Medical Center Board of Visitors, and the Johns Hopkins School of Nursing. Currently, she is a member of the Morehouse School of Medicine Board of Trustees, the Advisory Council of the University of North Carolina Gillings School of Global Public Health, and the Stakeholders Advisory Committee of the newly established Howard Hughes Institute K-RITH in Durban, South Africa.

Richard E. Chaisson, M.D., is Professor of Medicine, Epidemiology, and International Health, Center for TB Research, Johns Hopkins University School of Medicine and Bloomberg School of Public Health in Baltimore, Maryland. He received his B.S. and M.D. from the University of Massachusetts and was an intern, resident, and fellow at the University of California, San Francisco. From 1988 to 1998, he was director of the Johns Hopkins AIDS Service, and he co-founded with Richard Moore the Johns Hopkins HIV Clinic cohort, an observational cohort study that has made seminal contributions to understanding the outcomes of HIV disease and its treatment. In 1997, he founded the Johns Hopkins Center for Tuberculosis Research, a multidisciplinary institute dedicated to the study of TB from bench to bedside to community. His research interests focus on TB and HIV infection, including global epidemiology, clinical trials, diagnostics, and public health interventions. He is also Principal Investigator and Director of the Consortium to Respond Effectively to the AIDS/TB Epidemic, an international research consortium funded by BMGF to assess the impact of novel strategies for controlling HIV-related TB at the population level, including active case finding and widespread use of TB preventive therapy. In 2011, Dr. Chaisson was named Chair of the TB Transformative Science Group of the AIDS Clinical Trials Group and is leading the network's efforts in developing new TB therapeutic regimens. He maintains active collaborative research and training programs in Brazil, India, Lesotho, Malawi, and South Africa. Most recently, he assumed leadership of the Johns Hopkins Center for AIDS Research, re-establishing and revitalizing a transdisciplinary program to catalyze innovative HIV research at Hopkins, with a special focus on combating the Baltimore epidemic. He has published more than 400 scientific papers and book chapters.

Jin Chen, Ph.D., received his Ph.D. in immunology in 2005 from Fudan University. He then spent 5 years in the United States, obtained his postdoctoral training and Clinical Laboratory Technology license, and worked as faculty member in Mount Sinai School of Medicine. He went back to China in 2010 as the Chair of the Department of Clinical Laboratory Science, and Deputy Director, Shanghai Key Laboratory of Tuberculosis, Shanghai Pulmonary Hospital, Medical School, Tongji University. Dr. Chen has authored more than 30 research publications since entering the field. He is also the principal investigator of several research projects founded by the Chinese government.

Mingting Chen is Vice Director and Researcher, National Center for Tuberculosis Control and Prevention, China CDC. He received his master's degree in medicine from Beijing Union Medical College in 2000. In 1987, he joined the Department of Scientific Management, Chinese Academy of Preventive Medicine, which was renamed China CDC in 2002. From January 2000 to January 2002, he worked in the Department of Infectious Disease Management and Supervision of China CDC and then served as Vice Director of Office of China CDC. From 2006, Mr. Chen has been working in the National Center for Tuberculosis Control and Prevention of China CDC. As a leader of a research group, Mr. Chen is responsible for the study of a new type of anti-TB drug using anti-TB fixed-dose combination treatment in China. His specialties include health management, epidemiology, TB control and prevention (especially in MDR TB control and prevention programs), health promotion and training, and drug management.

Xiaoyou Chen, Ph.D., is Director and Chief Physician, Tuberculosis Department, Beijing Chest Hospital, Beijing Tuberculosis and Thoracic Tumor Research Institute. He received his B.S. from Anhui Medical University in 1993 and his Ph.D. from Beijing Tuberculosis and Thoracic Tumor Research Institute in 2003. He has been engaged in clinical diagnosis and treatment for patients with pulmonary TB and extrapulmonary TB since 1993. Dr. Chen conducted postdoctoral research on rapid screen mutation of a drug-resistant gene from *M.tb.* at Westmead Center for Infectious Diseases and Microbiology of Sydney University in 2007. His chief research areas are (1) new diagnostic marker screening in TBM, (2) rapid diagnosis of DR TB with gene mutation detection, and (3) treatment of pulmonary TB and extrapulmonary TB.

Dan Collins is a member of the Global Health Programs and Access Department, Corporate Affairs, Eli Lilly. He is leading the company's efforts to improve supply of and access to quality-assured second-line medications for MDR TB patients. Funded by the Eli Lilly & Co. Foundation, this effort

is designed to drive forward bold, action-oriented approaches; support new, innovative ideas and leverage Eli Lilly's internal assets, partnerships, and strong allies to advance progress. Mr. Collins is a certified Lean Six Sigma Black Belt and has led process and quality improvement and organizational effectiveness initiatives for Eli Lilly during the past 5 years. He is also accredited in public relations and has been responsible for external communications for many of Eli Lilly's pharmaceutical products. Before joining Eli Lilly, Mr. Collins provided crisis communications, marketing communications, and media relations counsel to clients in the health care industry and in a number of other private and not-for-profit sectors.

Jarbas Barbosa da Silva, Jr., M.D., Ph.D., M.P.H., has a degree in medicine from the Federal University of Pernambuco (1981), specialization degrees in public health (1984) and epidemiology (1989) from the National School of Public Health (Oswaldo Cruz Foundation/FIOCRUZ), a master's degree in medical sciences (M.P.H., 1995), and a doctorate in epidemiology (Ph.D., 2004) from the State University of Campinas. He was the Director of Health Surveillance and the Secretary of Health for the municipality of Olinda (state of Pernambuco, 1993–1994) and Secretary of Health for the state of Pernambuco (1995–1996). In 1997, he started a career in the Ministry of Health, Brazil, as Director of the National Center for Epidemiology (1997–2003); Secretary (Vice Minister) of Health Surveillance for the Ministry of Health (2003–2006); and Executive Secretary (Deputy Minister) for the Ministry of Health (second half of 2006). In 2007, Dr. Barbosa da Silva, Jr., joined the Pan American Health Organization (PAHO)/WHO in Washington, DC, as Area Manager of Health Surveillance, Prevention and Disease Control (January 2007–April 2010). In January 2011, he was appointed as Secretary (Vice Minister) of Health Surveillance, the Ministry of Health, Federative Republic of Brazil, which is his current position. Dr. Barbosa da Silva, Jr., is author or co-author of several articles and books on public health, epidemiology, surveillance, and disease prevention, control, and management. He has also participated as a speaker at national and international conferences and seminars and has been a member of the Brazilian delegation for international events such as WHO and the PAHO/WHO Regional Office for the Americas Direct Council.

Kathryn DeRiemer, Ph.D., M.P.H., is Associate Professor in the Departments of Public Health Sciences and Medical Microbiology and Immunology at the University of California, Davis, School of Medicine. Dr. DeRiemer received her M.P.H. and Ph.D. in epidemiology/biostatistics and epidemiology, respectively, from the University of California, Berkeley. She was a postdoctoral fellow in molecular epidemiology at Stanford University, California. Dr. DeRiemer is the recipient of an NIH Director's New Innovator

Award and is the Principal Investigator of an NIH/Fogarty International Center Global Infectious Diseases Research Training program with China. She has prior TB research experience in Brazil, India, and Mexico and has been working with collaborators at the Shanghai Municipal Centers for Disease Control and Prevention and Fudan University in China since 2006 to understand TB transmission dynamics and the spread and prevention of DR TB.

Min Fang, Ph.D., is Professor, Chinese Academy of Sciences Key Laboratory of Pathogenic Microbiology and Immunology, IMCAS. Dr. Fang received her Ph.D. from the Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, in 2003. She worked in the Fox Chase Cancer Center, Temple University, as a postdoctoral associate, research associate, and staff scientist before she joined IMCAS in June 2012 as a professor supported by the "Thousand Young Talents Program" of China's government. Her work has focused on studying the pathogenesis of viral infection using the ectromelia virus as a model, as well as the mechanisms by which vaccines afford protection. In this work she has uncovered important mechanistic insights into natural and acquired resistance to acute viral disease. Dr. Fang's work has been published in esteemed journals such as *Immunity*, *Journal of Experimental Medicine*, *Proceedings of the National Academy of Sciences of the United States of America*, and *PLoS Pathogen*. Multiple works were selected and referred to by the "Faculty of 1,000." One of the main research interests in Dr. Fang's laboratory is to investigate the role of natural killer (NK) cells in the control of *M.tb*. infection, especially the molecular mechanisms of NK cells recognizing *M.tb*.-infected cells and NK cell interaction with regulatory T-cells during infection.

Paul E. Farmer, M.D., Ph.D., is a medical anthropologist, physician, and Founding Director of Partners In Health, an international nonprofit organization that provides direct health care services and has undertaken research and advocacy activities on behalf of those who are sick and living in poverty. Dr. Farmer is Presley Professor of Social Medicine and Chair of the Department of Global Health and Social Medicine at Harvard Medical School, Chief of the Division of Global Health Equity at Brigham and Women's Hospital, and United Nations deputy special envoy for Haiti under special envoy Bill Clinton. Dr. Farmer and his colleagues in the United States and in Haiti, Lesotho, Malawi, Peru, Russia, and Rwanda have pioneered novel community-based treatment strategies that demonstrate the delivery of high-quality health care in resource-poor settings. Dr. Farmer has written extensively on health, human rights, and the consequences of social inequality. His most recent book is *Partner to the Poor: A Paul Farmer Reader*. Other titles include *Pathologies of Power: Health, Human Rights, and*

the New War on the Poor; *The Uses of Haiti, Infections and Inequalities: The Modern Plagues*; and *AIDS and Accusation: Haiti and the Geography of Blame*. Dr. Farmer is the recipient of numerous honors, including the Margaret Mead Award from the American Anthropological Association; the Outstanding International Physician (Nathan Davis) Award from the American Medical Association; a John D. and Catherine T. MacArthur Foundation Fellowship; and, with his Partners In Health colleagues, the Hilton Humanitarian Prize. He is a member of the IOM and of the American Academy of Arts and Sciences.

Neel R. Gandhi, M.D., is Associate Professor in the Departments of Epidemiology, Global Health, and Infectious Diseases at the Emory Rollins School of Public Health. Dr. Gandhi received his B.A. in chemistry from Williams College in 1994 and his M.D. in 1999 from Brown University School of Medicine. After completing his residency in internal medicine, Dr. Gandhi received epidemiology training at the Robert Wood Johnson Clinical Scholars Program at Yale University and infectious disease training at Emory University School of Medicine. He served on the faculty at Albert Einstein College of Medicine from 2006 to 2012. In July 2012, Dr. Gandhi joined the faculty at the Emory Rollins School of Public Health. Dr. Gandhi has been engaged in clinical research in TB and HIV co-infection since 1998. Since 2002, Dr Gandhi has led a research team focused on epidemiology and operational research studies to improve care for TB patients co-infected with HIV in KwaZulu-Natal province, South Africa. In 2006, Dr. Gandhi was the lead author on a study describing high rates of mortality in patients with XDR TB and HIV co-infection in the rural town of Tugela Ferry, KwaZulu-Natal. This study has been credited with uncovering a rapidly expanding MDR and XDR TB epidemic in South Africa. Since the discovery of the epidemic, Dr. Gandhi's efforts have been devoted to understanding the impact of HIV co-infection on the epidemiology, diagnosis, and treatment of MDR and XDR TB. His research group has definitively demonstrated that primary transmission of DR TB strains in health care and community settings are driving the rapid expansion of the epidemic. His group has also shown that the diagnosis of MDR TB is feasible in children, using bodily fluids other than sputum, and using the Microscopic Observation Drug Susceptibility assay in a resource-poor setting. In an effort to improve treatment capacity and outcomes, Dr. Gandhi's group developed an integrated, home-based treatment model for MDR TB and HIV, which is now being expanded nationwide in South Africa. Currently, Dr. Gandhi has grants from NIH/NIAID to examine the impact of concurrent antiretroviral and second-line TB therapy on survival, treatment outcomes, and adverse events for MDR TB and HIV, and to examine the transmission dynamics of XDR TB using molecular fingerprinting and social network analysis techniques.

George Fu Gao, Ph.D., is Vice Director General, China CDC, Beijing Institute of Biological Sciences, Chinese Academy of Sciences. Dr. Gao obtained his Ph.D. (D.Phil.) from Oxford University and completed his postdoctoral work at both Oxford University and Harvard University (with a brief stay at Calgary University). He is now Professor and Director in the Chinese Academy of Sciences Key Laboratory of Pathogenic Microbiology and Immunology, IMCAS. He is also the Vice President of Beijing Institutes of Life Science, Chinese Academy of Sciences; Deputy Director-General of China CDC; and Vice President of Chinese Society of Biotechnology. His research interests include the molecular mechanisms of interspecies transmission of pathogens, molecular virology, and molecular immunology. His group research focuses on the influenza virus, *Streptococcus suis*, and the molecular/structural basis of recognition of T-cell receptors to peptide-MHC complexes. He has published more than 190 refereed papers and 9 books or book chapters and has applied and obtained 20 UK, U.S., and Chinese patents.

Qian Gao, Ph.D., is Professor, Shanghai Medical College, Fudan University, China. Dr. Gao received his bachelor's degree from Southwest Agricultural University, China. He then completed his Ph.D. in molecular bacteriology at the University of Southern California and began TB research in 2000 during a postdoctoral fellowship at the Stanford University School of Medicine. Dr. Gao's research program on the transmission and pathogenesis of *M.tb.* incorporates national and international collaborations and includes research studies and training activities in China. Dr. Gao has more than 10 years' experience working with *M.tb.*, the disease it causes (TB), and other infectious diseases. Since 2004, Dr. Gao has been collaborating with researchers and public health professionals in China. His research focuses on the molecular epidemiology of TB, especially the transmission of this disease in China, and the genetic diversity and pathogenesis of Beijing genotype strains of *M.tb*. During the past several years, his team performed a prospective, population-based molecular epidemiological study of TB in China and found serious ongoing transmission of TB, especially MDR TB, in communities. His research results suggest that efforts to control TB, including MDR TB, must develop strategies to reduce the transmission of disease. He believes that novel strategies for the rapid diagnosis and control of recent transmission of *M.tb.* are essential for elimination of TB in China.

Maria Y. Giovanni, Ph.D., is Director, Office of Genomics and Advanced Technologies, and Assistant Director, Microbial Genomics and Advanced Technology, Division of Microbiology and Infectious Diseases, NIAID, NIH. Dr. Giovanni holds a Ph.D. in molecular biology from the University of Pennsylvania. She did her postdoctoral training in molecular

neuroscience in the NIH laboratory of Nobel Prize Laureate Dr. Marshall Nirenberg. She continued at NIH in 1988 at the National Eye Institute as Director of Fundamental Retinal Processes and then Chief, Retinal Diseases Branch, and she also led the institute's efforts in ocular genomics. In 2000, she moved to NIAID at NIH as Assistant Director for Microbial Genomics and Advanced Technologies and is now Director, Office of Genomics and Advanced Technologies. She has been involved in leading and managing genomics, bioinformatics, proteomics, and system biology programs in infectious diseases, including influenza, TB, malaria, human microbiome, other diseases, and biodefense and medical diagnostics for NIAID.

Anne E. Goldfeld, M.D., is Professor of Medicine at Harvard Medical School; Professor of Immunology and Infectious Diseases at Harvard School of Public Health; Senior Investigator in the Program in Cellular and Molecular Medicine, Children's Hospital Boston; Physician in the Division of Infectious Disease at Brigham and Women's Hospital; and Co-Founder of the Cambodian and Global Health Committees. She completed her medical internship, residency, and clinical fellowship in infectious disease at Massachusetts General Hospital and her postdoctoral work at Harvard University and the Dana-Farber Cancer Institute at Harvard Medical School before establishing her own laboratory at Harvard Medical School in 1992. Dr. Goldfeld's studies have led to paradigm-shifting insights into the function and regulation of the innate immune system, in particular, the transcriptional control of the tumor necrosis factor (TNF) gene. Work from her laboratory on the function of the TNF gene at the molecular level has demonstrated that transcriptional activation of the gene involves cell type– and stimulus-specific nucleoprotein complexes and chromatin organization, which has broad implications for eukaryotic gene regulation. Dr. Goldfeld has also made fundamental discoveries in the pathogenesis of HIV-1 and *M.tb*. She identified the first gene association with TB disease and was the first to identify the association of specific HLA-class I Bw4 alleles with HIV-1 control. Her characterization of immunosuppressive IL-10 producing T-cells in anergic TB was the first identification of a role for regulatory T-cells in infectious disease. Her laboratory has also made fundamental discoveries in how HIV is controlled at the level of transcription and has demonstrated that antigen-specific host-specific responses result in different patterns of HIV gene expression. Dr. Goldfeld's clinical work in Cambodia is marked by the innovative approach of nesting scientific studies within a clinical delivery network, and this has led simultaneously to major improvements in community-based models of care and international standards for treatment of patients suffering from HIV/TB co-infection in resource-poor areas, while at the same time elucidating the intricacies of the immune response during progression of these diseases

aimed at new therapeutics and cures. Recently, she and her colleagues have turned their attention to combating MDR TB in Ethiopia, where she helped establish the countrywide MDR TB Program in partnership with the Ethiopian Federal Ministry of Health. In addition to her scholarly scientific publications, her writing has appeared in the *New York Times*, the *Washington Post*, *The Nation*, the *International Herald Tribune*, the *Los Angeles Times*, and the *Boston Globe*.

Guangxue He, Ph.D., M.Sc., is Director of the Department of International Cooperation and Research, National Center for Tuberculosis Control and Prevention, China CDC. He also acts as the secretary and a member of the Disease Control Experts Committee for the Chinese Ministry of Health and is a standing member of the Beijing Anti-Tuberculosis Association, Vice-Director of the Chinese TB Ethical Committee, a member of the Editorial Committee of the *Journal of the Chinese Anti-Tuberculosis Association*, secretary and member of the Chinese TB Operational Research Management Committee, and Chief Manager of the Damien Foundation China TB Project, a WHO TB team consultant. Dr. He has been working in TB control and prevention for more than 20 years and has gained expertise in clinical practice, surveillance, monitoring and evaluation, epidemiology, and statistics, as well as control and prevention of MDR and XDR TB. Throughout his career, he has successfully designed, implemented, and conducted monitoring and evaluation within several national and international collaborative projects. He was involved in the nationwide random survey for the epidemiology of TB in China in both 2000 and 2010, as well as the nationwide anti-TB drug-resistant baseline surveillance in China in 2007. He is currently responsible for TB infection control, operational research and international cooperation, at the National Center for TB Control and Prevention, China CDC, and has published about 50 research articles and 7 books.

Sven E. Hoffner, Ph.D., is Director, WHO Supranational Tuberculosis Reference Laboratory; and Department for Preparedness, Swedish Institute for Communicable Disease Control. Dr. Hoffner defended his thesis on *Mycobacterium avium* and drug resistance at the Karolinska Institute in Stockholm. Thereafter, he got a position as Chief Microbiologist at the Swedish Institute for Infectious Disease Control (later renamed the Swedish Institute for Communicable Disease Control). His research has focused on DR *M.tb*. from a wide perspective, ranging from development and spread of DR strains, mechanisms of resistance, and development of improved tools for its detection to characterization of new targets for the next generation of anti-TB agents. He has published more than 160 scientific papers and has been the main supervisor for 10 Ph.D. students who successfully

defended their theses in the field of TB and mycobacteriology. He has a strong international commitment and holds the position of Director of the WHO Supranational Reference Laboratory in Stockholm. Dr. Hoffner is an Associate Professor in Medical Microbiology at the Karolinska Institute in Stockholm and holds the position of Director for the WHO Supranational Reference Laboratory for TB at the Swedish Institute for Communicable Disease Control in Solna, Sweden. His major research focus has been DR TB and mycobacteriology. He is involved in several international collaborations, mainly within the framework of WHO- or European Centre for Disease Prevention and Control (ECDC)-supported projects. His research group in Stockholm has evaluated and characterized new potential anti-TB drugs and studied their targets and antimycobacterial modes of action. Another topic for research has been the genetic background for drug resistance and the biological fitness costs related to it. Dr. Hoffner is a member of several scientific organizations and the editorial boards of four scientific journals, including the *International Journal of Mycobacteriology*.

Hairong Huang, Ph.D., is Deputy Director, National Clinical Laboratory on Tuberculosis, Beijing Chest Hospital. Dr. Huang received her Ph.D. in 2001 from the Beijing Tuberculosis and Thoracic Tumor Institute. She was a postdoctoral fellow from 2002 to 2006 in the Microbiology Department, Colorado State University. Dr. Huang has been involved in TB research since she was a Ph.D. student. Her main interests focus on laboratory diagnosis of TB and research on both an applied and basic track. On the applied track, she is trying to develop good diagnostics that are feasible for use in developing countries such as China and trying to answer questions that arise during patient health care. On the basic research side, her interests focus on drug resistance, gene function identification, pathogenicity analysis, and NTM.

Salmaan Keshavjee, M.D., Ph.D., Sc.M., is trained as a physician and an anthropologist. He is Director for the Program in Infectious Disease and Social Change in the Department of Global Health and Social Medicine at Harvard Medical School, where he is also Associate Professor of Global Health and Social Medicine and Associate Professor of Medicine. He is also a clinician in the Division of Global Health Equity at Brigham and Women's Hospital and a senior TB specialist at Partners In Health, an international nonprofit organization that provides direct health care services and advocates on behalf of those who are sick and living in poverty. Dr. Keshavjee has more than a decade of experience in the implementation of TB treatment programs in the former Soviet Union and southern Africa. His research is focused on improving treatment outcomes in patients with DR TB through programmatic interventions, as well as on understanding and improving policy responses to the global TB epidemic.

Liang Li is Office Director of the Clinical Center for Tuberculosis, China CDC, Office Director of the WHO Collaboration Centre for Training and Research on Tuberculosis, Vice-Director and General-Secretary of the Chinese Tuberculosis Society, and Chief-Director of the Beijing Chest Hospital. He received his bachelor's degree from Shandong Medical University (1987–1992), majoring in clinical medicine. He is working on TB control and is experienced in prevention, diagnosis, and treatment of TB, especially in regard to MDR TB and laboratory testing of TB. He was Vice-Director of the Administration Office of the National Drug-Resistance Survey in 2007–2008 and a key staff member of the 5th National TB Survey in 2010. He was Chief of the National 11th Five-Year Plan major scientific and technological Project on TB: The Study of Clinical Characteristics and Early Warning Models of DR-TB (ID:2008ZX10003-008-2); Technological Chief of the National 12th Five-Year Plan major scientific and technological Project on TB: Study of Treatment on DR-TB (ID:2013ZX10003-008); Chief of the Project on Bi-Directional Screening of Diabetes Mellitus and Tuberculosis in China Organization by the World Diabetes Foundation, The Union, and the Chinese TB Society; and Chief of the National Survey of Anti-TB Drugs Side-Effects in China.

Patrick Tao Li is Scientific Representative, BGI (formerly Beijing Genomics Institute). Mr. Li graduated with a bachelor's degree from South China University of Technology in 2010, the same year he joined BGI as a molecular breeding researcher. He contributed to the Balsa transgenetic system to induce species tolerance of the southeast Asian environment. In 2011, Mr. Li was appointed as Scientific Representative for BGI in France. He began managing collaboration between France and Africa on behalf of BGI in 2013.

Tao Li is Attending Physician and Assistant Director, Department of Tuberculosis, Shanghai Public Health Clinical Center, Fudan University. Dr. Li has engaged in clinical and scientific research on TB since 2010, with a focus on pediatric TB and MDR TB.

Megan B. Murray, M.D., M.P.H., Sc.D., is an epidemiologist and an infectious disease physician whose work focuses on the management of TB programs and TB epidemiology. After graduating from Dartmouth College in 1980, Dr. Murray worked with the Intergovernmental Committee for Migration in Thailand managing a TB screening program for refugees being resettled in other countries. She then attended Harvard Medical School and completed a residency in internal medicine at Massachusetts General Hospital, where she went on to specialize in infectious diseases and conducted research on methodological issues in TB epidemiology while obtaining her

M.P.H. and Sc.D. at the Harvard School of Public Health. Dr. Murray is a Professor in the Department of Global Health and Social Medicine at Harvard Medical School and an Associate Professor of Medicine and the Director of Research at the Brigham and Women's Hospital Division of Global Health Equity and its sister organization, Partners In Health. She is also an Associate Professor of Epidemiology at the Harvard School of Public Health, where she leads a research team that conducts multidisciplinary research on MDR and XDR TB involving conventional and molecular epidemiology, cost-effectiveness and mathematical modeling, outcomes and operations research, and genomic epidemiology. She has conducted field studies in Peru, Russia, Rwanda, South Africa, and the United States and has previously worked in Kenya, Niger, and Pakistan. Dr. Murray serves as an editor for *PLoS Medicine* and for the *European Journal of Epidemiology*. She is a member of WHO's TB-Strategic and Technical Advisory Group, the Stop TB MDR Working Group, and the WHO Global XDR-TB Task Force. She has also served on numerous other committees, including the Harvard University Human Subjects Committee, the Harvard Pandemic Flu Advisory Committee, the IOM committee on Gulf War and Infectious Diseases, and NIH study sections.

Edward A. Nardell, M.D., is Associate Professor, Division of Global Health, Brigham and Women's Hospital, Harvard Medical School. Dr. Nardell 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, positions he held until 2005. His principal academic appointment is 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 Partners In Health 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 Partners In Health. 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 HBCs. His special research interest is airborne TB transmission and control. Currently, he has a project in South Africa, funded by National Institute of Occupational Safety and Health, studying the transmission of MDR TB using large numbers of guinea pigs to quan-

tify the infectiousness of MDR TB patients and the effectiveness of various control interventions, including UVGI. Dr. Nardell is past president of the Massachusetts Thoracic Society and The Union, North American Region. He was the 2005 recipient of the Chadwick Medal of the Massachusetts Thoracic Society.

Mark Nicol, M.D., Ph.D., is the Wernher and Beit Professor and Head of the Division of Medical Microbiology, University of Cape Town and National Health Laboratory Service of South Africa. He directs an academic diagnostic microbiology laboratory as well as a research laboratory where TB diagnostic assay development and evaluation takes place. He has worked closely with the Foundation for Innovative New Diagnostics and the TB Clinical Diagnostics Research Consortium in the evaluation of novel diagnostics for TB, from early-stage performance studies to studies evaluating clinical impact.

Dale Nordenberg, M.D., is Chief Executive Officer of Novasano Health and Science, a company that delivers services and products to accelerate innovation in health care and life sciences with a particular focus on leveraging the strategic application of information resources. He co-founded and is directing a public–private partnership based at the U.S. CDC Foundation that includes numerous initiatives to build laboratory information management capability for DR TB, including genomic foundations for resistance. He is also the Co-Founder and Executive Director for the Medical Device Innovation, Safety, and Security Consortium—a public–private partnership that works to improve the security and safety of medical devices. Prior to Novasano, Dr. Nordenberg was a managing director in the health care practice of PricewaterhouseCoopers. From 2002 through 2007, Dr. Nordenberg held various positions at U.S. CDC, including Chief Information Officer and Associate Director, National Center for Infectious Diseases. He was detailed to the Office of the National Coordinator for Health Information Technology at the Department of Health and Human Services in 2004–2005 to catalyze the development of a national strategy for children's health information technology. Dr. Nordenberg has been a member of the Science and Technology Review Subcommittee of the Science Advisory Board of FDA, 2007 and 2009. Prior to joining U.S. CDC, Dr. Nordenberg was a founding executive of a company that launched VeriSign affiliates in Latin America and Asia; prior to that, he was faculty in the Emory School of Medicine, where he founded and directed the Office of Medical Informatics for the Emory University Children's Center. Dr. Nordenberg has served on the boards of multiple companies. He is a board-certified pediatrician; received a B.S. in microbiology from the University of Michigan and an M.D. from Northwestern University, and completed his training in pediat-

rics at McGill University, Montreal Children's Hospital, and his fellowship in epidemiology and public health in the Epidemic Intelligence Services Program at U.S. CDC.

Carol Rao, Sc.D., M.S., CIH, joined the U.S. CDC International Emerging Infections Program, Global Disease Detection, China Office, to serve as the Chief of the Epidemiology Section in September 2009. In this position, she collaborates with China CDC to provide technical support for public health projects in China, with a particular focus on TB infection control and health care–associated infections. Since 1999, Dr. Rao has worked as an epidemiologist and industrial hygienist at U.S. CDC in several of its centers, conducting research on infectious and noninfectious respiratory diseases. Her work has included implementing a national surveillance system for influenza vaccination among health care workers, investigating mycotic disease outbreaks in hospital and community settings, and conducting exposure assessments for indoor microorganisms in relation to work-related asthma. Her research interests include infectious aerosols, infection control, health care–associated infections, and controlling transmission of respiratory diseases, such as TB. Dr. Rao received an undergraduate degree in biophysics from the University of California, Berkeley, and an M.S. in industrial hygiene and a Sc.D. in environmental health from Harvard University School of Public Health. She received postdoctoral training at the Finnish National Public Health Institute in Kuopio, Finland, as a Fulbright Fellow and at U.S. CDC as an Epidemic Intelligence Service Officer. Dr. Rao is board-certified in industrial hygiene. Dr. Rao has twice received the Department of Health and Human Services Secretary's Award for Distinguished Service, as well as numerous U.S. Public Health Service commendations and medals for her work on outbreaks and emergency response.

Fabio Scano, M.D., is a Medical Officer, WHO Tuberculosis Program, China. Dr. Scano, a medical doctor and public health specialist, is a Team Leader within WHO in Beijing, responsible for the organization's TB control program in China, which has one of the highest burdens of MDR TB. He began his career with WHO in 2001 in the Stop TB Department, where he helped develop policies to provide diagnosis and care to those co-infected with both TB and HIV in low- and middle-income countries. In 2007, Dr. Scano was deployed to South Africa to assist the Department of Health in the response to the XDR TB outbreak in Tugela Ferry. Upon his return to WHO headquarters, Dr. Scano coordinated the development of the WHO policy on TB infection control. Dr. Scano, a former Yale World Fellow, also collaborates with the Aspen Institute on initiatives aimed at alleviating "brain drain" in Italy, a phenomenon in which talented young Italians leave the country in search of better opportunities.

Oskar Slotboom is the Business Unit Head, Vaccines and Infectious Diseases, of Xian Janssen Pharmaceutical Ltd., a pharmaceutical company of Johnson & Johnson. Prior to joining Johnson & Johnson, Mr. Slotboom worked for Crucell in the Netherlands, a biotech company focusing on innovative vaccines and biologics for the treatment of infectious diseases. Crucell was acquired by Johnson & Johnson in 2011. At Crucell, Mr. Slotboom was responsible for the pediatric vaccine franchise that included the best-selling vaccine (Quinvaxem) for UNICEF under GAVI funding at the time. He also worked as a consultant at McKinsey & Company in Amsterdam. Mr. Slotboom holds a master's degree in chemical engineering from the University of Twente, the Netherlands, and received an M.B.A. from INSEAD, Fontainebleau, France.

Yao-Ju Tan is Director of the Clinical Laboratory Department of Guangzhou Chest Hospital. He is primarily engaged in basic research of *M.tb*. In 1998, he was a Visiting Scholar in the Department of Microbiology of Hong Kong University. He then was at in the College of Life Sciences of Wuhan University, where he obtained his master's degree in 2002. Currently, Mr. Tan serves as the Associate Director of the Basic Research Board of the Chinese Anti-TB Association, as the Technical Specialist of the TB Project of BMGF of the Ministry of Health, China, and as the Associate Director of Microbiology and Immunology of Guangdong Province Phylaxiology Association. He is also a member of the Guangdong Medical Ecsomatics Association. In addition, he has taken charge of or participated in research programs including the National Great Research Program of China (2008zx10003-009) and has published many research papers in the past 2 years.

Carrie Tudor, Ph.D., M.P.H., R.N., attended Indiana University with a double major in Chinese language and political science. She later attended the Rollins School of Public Health at Emory University, where she earned her M.P.H. After Emory, she worked for more than 10 years on various international health projects in Cambodia, China, India, Myanmar, and South Africa. Dr. Tudor has worked in infection control for several years and trains nurses on TB and infection control in several countries for the International Council of Nurses. She has conducted research on infection control in MDR and XDR TB facilities throughout South Africa and has studied health care worker infection control knowledge. Dr. Tudor recently completed her Ph.D. at the Johns Hopkins University School of Nursing with a focus on occupational risk factors for TB among health care workers in South Africa and is currently a Fogarty Global Health Postdoctoral Fellow at Johns Hopkins School of Nursing, University of North Carolina at Chapel Hill. She is passionate about improving the protection of health care workers in low-resourced settings.

Zarir F. Udwadia, M.D., FRCP, FCCP, is a Consultant Chest Physician, Medical Research Council, Hinduja Hospital and Research Center, Mumbai. In postgraduate studies at Grant Medical College, Bombay, he spent 5 years training in various centers of excellence in the United Kingdom, including Sir John Crofton's former TB unit in Edinburgh and the prestigious Brompton Hospital, London. On his return, he established an active chest department at the Hinduja Hospital, a tertiary referral center in Mumbai. He has a special interest and expertise in DR TB. About 7,000 patients pass through his busy outpatient department (OPD) annually, a number of whom are MDR TB patients referred by colleagues from different parts of the country. TB remains his overriding passion. Dr. Udwadia has been invited to lecture on TB in several countries, including guest orations before the British Thoracic society, ERS, the International Union, the American College of Clinical Pharmacy, and the Royal Society of Medicine in London. He was invited to deliver the inaugural lecture on "Tackling MDR and XDR TB in Resource-Limited Settings: India" at the Gordon TB drug discovery conference, Oxford, United Kingdom, in 2009 and the inaugural lecture at the TB conference at Harvard Medical School on TDR TB in 2012. He was the only Indian invited to be on the WHO "Guidelines Group." This group, after meetings in Paris, formulated the fourth edition of the TB Guidelines, published by WHO in 2010. Dr. Udwadia's group was the first to publish data on the survival of a large cohort of Indian MDR TB patients treated on an OPD basis at the Hinduja Hospital, which showed that this group of patients could be treated even in difficult, cost-constrained settings with success rates of more than 60 percent. His group was also the first to report fluoroquinolone-resistant and XDR TB in India. His recent publication about the first Indian patients with TDR TB attracted intense media and medical interest from across the globe. He was invited by WHO to Geneva in March 2012 to be part of the technical group to determine the most appropriate nomenclature and treatment for these patients. His work on TDR TB served to galvanize great change in the community. The Indian health authorities responded by declaring TB a notifiable disease on May 7 and increasing the budget and staffing for TB control in the city. With the sanction of government health authorities and at the invitation of the Indian Health Secretary, he has set up a public–private DOTS-Plus clinic in Dharavi (Asia's largest slum), where he devotes his time on a voluntary basis. This clinic will be the first of its kind in the city of Mumbai, and it is hoped that it will serve as a model for the MDR TB public–private mix in the National TB program. Dr. Udwadia has more than 80 PubMed-indexed publications to his credit, and his book *Principles of Respiratory Medicine* has just been published by Oxford International Publishers (2011). His chapters on "Tuberculosis in India" and "Drug-Resistant TB in India" have been featured in several

editions of *Clinical Tuberculosis*, the standard textbook of TB (edited by P.D.O. Davies). Dr. Udwadia is actively involved in ongoing TB research collaborations with partners from across the globe. These projects include new TB diagnostics (with colleagues at the Imperial College London) and new TB drugs (with colleagues in Japan, Portugal, and the United States). He is currently the section editor for TB for the journal *Thorax*.

Martie van der Walt, Ph.D., M.B.A., is the Interim Director of the Tuberculosis Epidemiology and Intervention Research Unit of the South African Medical Research Council and Extraordinary Professor in the Department of Internal Medicines, Faculty of Health Sciences, University of Pretoria, South Africa. The unit conducts research on infection control, the epidemiology of DR TB, treatment adherence, and TB/HIV integration through the program for Tuberculosis HIV/AIDS Treatment Support and Integrated Therapy. The WHO/The Union Tuberculosis Supranational Reference Laboratory for Africa is also housed by Dr. van der Walt's unit, whereby technical assistance in TB laboratory capacity is provided to southern African countries and to the National Health Laboratory Service in South Africa. Dr. van der Walt is specifically interested in the programmatic delivery of DR TB treatment and treatment adherence. Prior to working for the Medical Research Council, she was involved in animal health and obtained her Ph.D. in vaccine development and biotechnology.

Grigory V. Volchenkov, M.D., is TB Infection Control Expert and Chief Doctor at Vladimir Oblast Regional Tuberculosis Dispensary, Center of Excellence for TB Infection Control. He graduated in 1985 from Ivanovo State Medical Institute, Russia. Dr. Volchenkov worked in Vladimir Cardiology Hospital as a cardiologist, intensive cardiology care specialist, and medical director from 1985 to 1999. From 1999 to 2002, he worked for the Vladimir Oblast Department of Health as Chief Internal Medicine Specialist. At that time, he started to coordinate regional TB and HIV control programs. Since 2002, he has been the Head of Vladimir Regional Tuberculosis Dispensary and Director of the regional TB control program. In 2002–2003, he moved the dispensary to a new building and implemented an intensive TB infection control program supported by U.S. CDC, the WHO TB control program in the Russian Federation, and the Central TB Research Institute (Moscow), resulting in substantial reduction of occupational TB among health care workers. In 2008, Vladimir Oblast TB Dispensary became a Center of Excellence for TB Infection Control for the Russian Federation. Dr. Volchenkov is co-author of the national TB Infection Control Guidelines of several Eastern European and Central Asian countries. He coordinated and chaired TB infection control–related symposia and sessions at the IUATLD World and European Conferences

from 2005 to 2012, dedicated to TB case findings, DR, MDR and XDR TB epidemiology, and TB infection control. He also coordinated and lectured in postgraduate courses on TB infection control from 2006 to 2012 at the Annual World IUATLD Conferences. Since 2006, he been implementing a GLC-approved MDR TB project at Vladimir Oblast. The TB Alliance included Vladimir Oblast TB Dispensary in a list of potential research and trial centers. Dr. Volchenkov is a regional coordinator of a multicenter international PETTS (Preserving Effective TB Treatment) Study. He participated as a faculty member in a Harvard University continuing education course, *Building Design and Engineering Approaches to Airborne Infection Control*, held in Boston, Massachusetts, in 2008–2012. Dr. Volchenkov was invited by WHO, the Finnish Lung Health Association, the KNCV Tuberculosis Foundation, Médicins Sans Frontières, and other international organizations to lecture on TB infection control in Amaty, Armenia, Ashgabat, Estonia, Kazakhstan, Minsk Belarus, Moscow, Petrozavodsk, St. Petersburg, Tartu, Turkmenistan, Yerevan, and other regional centers of Russia. As a TB infection control consultant, Dr. Volchenkov conducted WHO technical assistance missions to Armenia, Azerbaijan, Chechnya, Myanmar, Nepal, Tajikistan, Turkmenistan, Ukraine, and other countries.

Kristina Wallengren, Ph.D., M.P.H., is Clinical Advisor, K-RITH, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal; and Chief Executive Officer, THINK. Dr. Wallengren has 20 years of research experience ranging from basic science to clinical research. She conducted molecular and cellular virology research at Karolinska Institutet in Sweden (1991–1998) and at Centro Nacional de Biotechnologia in Spain (1998–2001). She then ventured into the field of clinical research on TB and HIV after studying international health at the Harvard School of Public Health, where she also completed postdoctoral studies in the Department of Epidemiology. Since 2005, Dr. Wallengren has been based in South Africa, where she started conducting research on risk factors for TB and adherence to HIV treatment with Harvard. In 2007, she was recruited by WHO to conduct an analysis of DR TB in the KwaZulu-Natal province following an outbreak of XDR TB in Tugela Ferry (Ghandi et al., *Lancet*, 2006). This work led her to introduce community-based MDR TB treatment for the first time in the country, and she is currently following a cohort of 800 MDR TB subjects to evaluate the impact of the new program compared to hospital-based treatment. Since 2010, Dr. Wallengren has headed clinical research at K-RITH in Durban, South Africa, and is engaged in conducting clinical trials to improve TB treatment as well as developing new diagnostics tools for TB. Dr. Wallengren earned a Ph.D. in cellular and molecular biology from Karolinska Institute and an M.P.H. from the Harvard School of Public Health.

Pang Yu, Ph.D., is Associate Professor, National Tuberculosis Reference Laboratory, National Center for Tuberculosis Control and Prevention, China CDC. Dr. Yu received his Ph.D. in 2009 from Peking University. Since 2009, he has been involved with the National Tuberculosis Reference Laboratory. His research focuses on the mechanism of drug resistance in TB, the molecular epidemiology of TB in China, and evaluation of new diagnostic tools for TB. Dr. Yu is a committee member on the Basic Research Board of the Chinese Anti-Tuberculosis Association. He has authored more than 20 research publications since 2009.

Jack Zhang, M.S., M.B.A., represents PATH (an international nonprofit organization that transforms global health through innovation) in China. He is responsible for program development, project management, office management, and liaising with local and international collaborators, including local health authorities, public and private institutions, and other NGOs in China. Mr. Zhang joined PATH in January 2007 as senior program officer for commercialization of the Ultra Rice® project in China and was appointed as program leader in September of the same year. Before joining PATH, he created and served as Chief Representative and General Manager of Haemoneitics China Subsidiary, a Boston-based blood-processing company. Prior to that, Mr. Zhang worked in the Shanghai Institute of Biological Products, a subsidiary of China National Biotec Group, where his last position was Executive Vice President for Operations. During his tenure at the Shanghai Institute of Biological Products, he also served as Director of the Board of SmithKline Beecham Biologicals (Shanghai) Co., Ltd., and as Vice Chairman of the board of Shanghai Feilong Medical Diagnostic Articles Ltd., a joint venture between the Shanghai Institute of Biological Products and the Lab System Company of Finland. His areas of management experience include strategy, organization building, and business development and commercialization of vaccines, plasma-derived products, diagnostics, and medical devices in transfusion therapy. Mr. Zhang obtained a diploma in public health from Shanghai Songjiang Health School, a B.A. in French and English from Shanghai Fudan University, a master of library and information sciences specializing in medicine from a joint program of Dominican University and Loyola Medical School, and an executive M.B.A. from the China European International Business School.

Lixin Zhang, Ph.D., is a Deputy Director, Chinese Academy of Sciences Key Laboratory of Pathogenic Microbiology and Immunology; and Inaugural Director, Drug Discovery Center for Tuberculosis, IMCAS. Before joining IMCAS in 2006, Dr. Zhang worked in three pharmaceutical companies in the United States: SynerZ, Cetek, and Microbia, Inc. He received his Ph.D. at the Institute of Applied Ecology, Chinese Academy of Sciences, and did

his postdoctoral work at Emory University. He has published 7 books and more than 100 papers and holds 12 Patent Cooperation Treaty patents. Dr. Zhang co-edited a book with Arnold Demain on natural products, published in 2005 by Humana Press. He served as an Executive Board Member of the International Symposium on the Biology of Actinomycetes and of the International Chemical Biology Society. He was recognized as an honorary lifetime member, Sino-American Pharmaceutical Professional Association. He has been appointed as an Associate Editor-in-Chief for *Applied Microbiology and Biotechnology* and is on the editorial board of six other peer-reviewed journals. The long-term goal of his research is to discover and develop synergistic medicines from marine microbial natural products. His research is focused on diversifying the marine microbial natural product library; screening for synergistic medicines in a high-throughput manner; and increasing the production of drugable secondary metabolites from microbial producers by synthetic biology (as chief principal investigator for a 973 program). Dr. Zhang's Avermectin project won an award for "Excellence to Improve Science and Technologies," and the paper was published in *Proceedings of the National Academy of Sciences of the United States of America*. Dr. Zhang was recognized as an awardee for the National Distinguished Young Scholar Program, China.

Wenhong Zhang, M.D., Ph.D., is Professor of Medicine and Director, Division of Infectious Diseases, Shanghai Huashan Hospital of Fudan University. Dr. Zhang graduated from Shanghai Medical University and was appointed as a tenured professor of Fudan University in 2007 and as the Director of the Department of Infectious Diseases of Huashan Hospital, affiliated with Fudan University, in 2010. In 2001, Dr. Zhang began postdoctoral training in the Department of Microbiology at Hong Kong University. In 2003, he was appointed to the position of research fellow at Beth Israel Deaconess Medical Center, affiliated with Harvard Medical School. In 2006, he worked as Senior Visiting Scholar in the Department of Microbiology and Immunology at the University of Illinois, Chicago. He has been engaged in clinical, educational, and research work relating to infectious diseases for more than 20 years and is an expert in the diagnosis and treatment of infectious diseases, especially HIV and TB co-infection. Dr. Zhang's team focuses its research on the pathogenesis, diagnosis, and treatment of MDR TB and latent TB as well as HIV and TB co-infection.

Yaping Zhang is the Vice President of the Chinese Academy of Sciences. Dr. Zhang graduated from Fudan University with a bachelor's degree in 1986 and from Kunming Institute of Zoology (KIZ) of the Chinese Academy of Science with a doctorate in 1991. He then became a postdoctoral fellow at the Zoological Society of San Diego's Center for Reproduction of

Endangered Species for 4 years. Following this, he returned to China and worked as Professor and Director of Laboratory of Cellular and Molecular Evolution at KIZ. In 2002, Dr. Zhang was appointed Professor and Head of the Laboratory of Genetics, Yunnan University. From 2005 to 2012, he was Director of KIZ and Director of the State Key Laboratory of Genetic Resources and Evolution, KIZ. He was nominated as Vice President of the Chinese Academy of Sciences in 2012. As a Research Professor at KIZ, he has been focusing on molecular evolution and genome biodiversity. His investigations involve five correlated areas: (1) molecular phylogenetics; (2) molecular ecology and conservation genetics; (3) human genetics and evolution; (4) origin of domestic animals and artificial selection; and (5) genome diversity and evolution. Dr. Zhang has published more than 300 publications in Science Citation Information journals and is the author and co-author of 5 books. He was elected as a member of the American Society of Human Genetics in 1996, the Society for Molecular Biology and Evolution in 1997, and the American Genetic Association in 1998. He was elected Vice President of the Chinese Society of Genetics in 2004, Vice President of the Chinese Society of Zoology in 2005, and President of the Yunnan Association for Science and Technology in 2008. Dr. Zhang sits on the editorial boards for several international periodicals, including *Genome Biology and Evolution* and *Animal Genetics*. Dr. Zhang has won dozens of natural science prizes in China, including the Ho Leung Ho Lee Prize for Science and Technology from the Ho Leung Ho Lee Foundation in 2004. He was elected as a member of the Chinese Academy of Sciences in 2003 and as a fellow of the Third World Academy of Sciences in 2007.

Yanlin Zhao, M.D., Ph.D., is Vice Director, National Center for Disease Control and Prevention, and Director, National Tuberculosis Reference Laboratory, China CDC. His research areas include TB, molecular epidemiology, drug resistance surveillance, and new diagnostics. His activities include serving as principal investigator for the study of the Chinese TB prevalence mechanism (National Key Research Project 2008–2010); the new diagnostic evaluation in China (BMGF Project, 2009–2014); and the laboratory new diagnostics validation program (Fondation Mérieux, 2007–2011). He also served as principal investigator of a nationwide anti-TB drug resistance baseline survey in China (2005–2008) and as principal investigator of five projects (Beijing Natural Scientific Research Fund/Beijing Scientific Research Star projects, etc. [2005–2008]).