The New Profile of Drug-Resistant Tuberculosis in Russia: A Global and Local Perspective: Summary of a Joint Workshop

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The New Profile of Drug-Resistant Tuberculosis in Russia

A Global and Local Perspective

SUMMARY OF A JOINT WORKSHOP
by the Institute of Medicine and the Russian Academy of Medical Science

Steve Olson, Rebecca English, and Anne Claiborne, *Rapporteurs*

Forum on Drug Discovery, Development, and Translation

Board on Health Sciences Policy

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Willing is not enough; we must do."
—Goethe

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

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by

Dr. Melvin Worth. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authors and the institution.

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Acronyms

AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
BCG	Bacillus Calmette-Guérin vaccine
CD4	Cluster of Differentiation 4
CDC	Centers for Disease Control and Prevention
CTRI	Central Tuberculosis Research Institute
DNA	deoxyribonucleic acid
DOTS	Directly Observed Treatment Short course
FDA	Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
GDF	Global Drug Facility
GLC	Green Light Committee
GLI	Global Laboratory Initiative
GMP	Good Manufacturing Practices
HIV	human immunodeficiency virus
IL-7	interleukin-7
IOM	Institute of Medicine
ISTC	International Science and Technology Center

ISTC	International Standards for Tuberculosis Care
LPA	line probe assay
M.tb.	*Mycobacterium tuberculosis*
MDR TB	multidrug-resistant tuberculosis
MRSA	methicillin-resistant Staphylococcus aureus
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NTM	nontuberculosis mycobacteria
PCR	polymerase chain reaction
PETTS	Preserving Effective Tuberculosis Treatment Study
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PPD	purified protein derivative
RAMS	Russian Academy of Medical Sciences
TB	tuberculosis
TDR TB	totally drug-resistant tuberculosis
USAID	U.S. Agency for International Development
UV	ultraviolet
WHO	World Health Organization
XDR TB	extensively drug-resistant tuberculosis

1

Introduction[1]

An estimated 2 billion people, one-third of the global population, are infected with *Mycobacterium tuberculosis (M.tb.),* the bacterium that causes tuberculosis (TB) (Keshavjee and Seung, 2008). Spread through the air, this infectious disease killed 1.7 million people in 2009, or approximately 4,700 each day (WHO, 2010a). TB is the leading killer of people with HIV, and it is also a disease of poverty—the vast majority of TB deaths occur in the developing world (WHO, 2010a). Exacerbating the devastation caused by TB is the growing threat of drug-resistant forms of the disease in many parts of the world. Identifying and addressing barriers to effective and timely diagnosis and treatment of drug-resistant TB will be critical to preventing the further emergence of strains of TB with broad-spectrum resistance (Keshavjee and Seung, 2008). The workshop summarized in this volume, held in Moscow, Russian Federation, was the second international

[1]The workshop was organized by an independent planning committee whose role was limited to the identification of topics and speakers. While the Institute of Medicine's (IOM's) Forum on Drug Discovery, Development, and Translation conceived the idea for this workshop, this summary was prepared by the rapporteurs as a factual summary of the presentations and discussions that took place at the workshop. Statements, recommendations, and opinions expressed are those of the individual presenters and participants, are not necessarily endorsed or verified by the Drug Forum or the National Academies, and should not be construed as reflecting any group consensus.

meeting in a series designed to gather information from experts around the world on the nature of this threat and how it can be addressed.[2]

THE PROBLEM OF DRUG RESISTANCE

The development of drug resistance is a predictable, natural phenomenon that occurs when microbes adapt to survive in the presence of drug therapy (Nugent et al., 2010). Although antibiotics developed in the 1950s are effective against a large percentage of TB cases, resistance to these first-line therapies has developed over the years, resulting in the growing emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB (see Box 1-1 for definitions). Workshop participants noted that the rapid spread of drug-resistant forms of TB poses new challenges to effective control of this disease, as diagnosing and effectively treating MDR/XDR TB patients requires increasingly complex public health interventions. MDR TB, for example, is resistant to first-line drugs and must be treated with second-line drugs that are more expensive and more toxic, often require injection, and involve longer treatment regimens (2 years or more to treat MDR TB compared with 6–9 months to treat drug-susceptible TB). As drug resistance develops, the challenge is to preserve the effectiveness of current drugs and create new treatment regimens to combat resistant strains as they emerge.

During the workshop, Paul Farmer, founding director of Partners In Health, noted that although the advent of diseases such as drug-resistant TB, methicillin-resistant *Staphylococcus aureus* (MRSA), and extensively drug-resistant malaria was inevitable, it is possible to change the course of these epidemics and the rate at which acquired and transmitted resistance to the drugs used to treat those infected takes hold in a population.

THE BURDEN OF DRUG-RESISTANT TB

Based on global drug resistance surveillance data from the World Health Organization (WHO), it is estimated that 3.6 percent of global TB cases, or a total of 440,000 cases, were MDR TB in 2008 (95 percent confidence interval, 390,000–510,000) (WHO, 2010b). However, a number of TB experts at this and prior workshops explained that available data on drug-resistant TB are inadequate and yield a gross underestimation of the true global burden of disease (see Chapter 2). Surveillance systems

[2]The Drug Forum held a foundational workshop in Washington, DC, in 2008. The summary of that foundational workshop, *Addressing the Threat of Drug-Resistant Tuberculosis: A Realistic Assessment of the Challenge: Workshop Summary,* and the accompanying white paper (Keshavjee and Seung, 2008) provided background for and informed the development of and proceedings at the Russian Federation workshop summarized in this volume.

BOX 1-1[a]
The Nature of the Threat

Definitions

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

Extensively drug-resistant tuberculosis (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 tuberculosis (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.

Treatment

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

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

do not exist or are not capable of valid and reliable reporting in many developing countries where the MDR TB burden is likely to be substantial. Even the most recent global surveillance data on MDR TB do not include 79 countries—41 percent of all countries in the world (WHO, 2010b, p. 6). According to WHO, although the estimate of 440,000 MDR TB cases for 2008 indicates a decrease relative to 2006 (best estimate of 489,000 cases), this change reflects the reporting of new data, changes in TB incidence, and the use of updated diagnostic methods and should not be considered reflective of a true decline in MDR TB cases (WHO, 2010b, p. 18).

Data on the burden of XDR TB are even more limited because many countries lack the laboratory and infrastructure capacity necessary to test MDR TB patients routinely for susceptibility of their infection to second-line drugs. Unfortunately, moreover, the drug susceptibility testing that many countries are ill equipped to conduct is the basis for providing optimal patient care for MDR and XDR TB patients. It is through such testing that physicians determine which drugs are likely to be effective against a particular drug resistance profile (the relationship between drug susceptibility testing and treatment is further discussed in Chapter 6). A number of workshop participants noted that the vast majority of MDR and XDR TB cases are undetected and thus untreated with appropriate second-line drugs. Among the small proportion of patients who are being treated with second-line drugs, many are not taking the right drugs to treat their drug resistance profile effectively (see the section "Remaining Challenges" in Chapter 2 for a discussion of the estimated proportion of MDR TB patients receiving care and the challenges to providing quality-assured second-line drugs for patients that need them).

Overall, Russia has experienced a high burden of MDR TB in recent decades. Fluctuations in the level of disease in the population have mirrored the social, political, and economic upheavals in the country. For instance, the dissolution of the Soviet Union eliminated stringent federal control over TB prevention and treatment programs across the vast country. This loss of control over TB programs was accompanied by increased unemployment, poverty, population displacement, crime rates, and military conflicts, all of which exacerbated the spread of TB (see Chapter 3 for additional historical background on TB control in Russia).

WORKSHOP OBJECTIVES

The workshop summarized in this volume is part of a series on drug-resistant TB being conducted by the Forum on Drug Discovery, Development, and Translation of the Institute of Medicine (IOM). The workshop was held May 26–27, 2010, in collaboration with the Russian Academy of

Medical Sciences (RAMS) and held at the International Science and Technology Center (ISTC) in Moscow, Russian Federation.

The first workshop in this series took place in Washington, DC, on November 5, 2008 (IOM, 2009) and led to plans for four additional workshops in countries with a high burden of drug-resistant TB. The first international workshop in the series was held in Pretoria, South Africa, on March 3-4, 2010 (IOM, 2011). Future workshops are being planned for China and India.

In a broader context, this workshop in Moscow was also the first in a series that will occur over the next 5 years on biomedical research and health issues of the highest priority between the United States and Russia. This series grew out of a Memorandum of Understanding signed between Presidents Barack Obama and Dmitry Medvedev at their summit in July 2009, a date that also marked the 50th anniversary of collaboration between the Russian Academy of Sciences and the U.S. National Academy of Sciences. The workshop brought together about 100 disease experts, community leaders, policy makers, and patient advocates from Russia, the United States, South Africa, and China for 2 days of intensive discussions. The workshop was supported in part by the U.S. Department of State.

The objectives of the workshop were to learn from the historical and contemporary experiences of the Russian public health community in its efforts to control and combat the spread of drug-resistant TB, and to draw lessons regarding best practices and novel approaches that can be applied in the region and across the globe. An important objective of the presentations and discussions among workshop speakers and guests was to forge new linkages and collaborations across multiple disciplines and countries and facilitate the sharing of scientific knowledge to benefit TB control efforts. Specifically, the workshop was designed to:

- increase awareness and create a renewed sense of urgency with respect to the growing global burden of MDR and XDR TB and its profile in Russia;
- consider the magnitude of transmission of drug-resistant strains and options for control of transmission and infection;
- address the MDR TB burden in vulnerable populations, including children, those coinfected with HIV, and substance abusers;
- assess current treatment options and approaches to patient care, taking into account the unique needs of the population being treated;
- discuss the supply of quality-assured second-line TB drugs and the pipeline for a new "cocktail" of TB drugs;
- assess the current state of the art for rapid detection of drug resistance and the implications for patient management; and

- suggest policies for accelerating improvements in treatment and infection control for drug-resistant TB.

A REALISTIC ASSESSMENT OF THE CHALLENGES OF DRUG-RESISTANT TB

Gail Cassell, Forum co-chair, Eli Lilly and Company (retired), provided opening remarks to set the stage for the workshop. She summarized major themes from the Drug Forum's foundational 2008 workshop and the March 2010 workshop in Pretoria, South Africa, both of which focused on understanding and addressing the realistic challenges of drug-resistant TB globally and in country.

Drug-resistant TB is a global challenge, but (as noted above) global estimates of the burden of disease grossly underestimate the magnitude of the MDR and XDR TB problem. Given the limitations of surveillance systems in many developing countries, statistical models are often used to derive the estimated burden of TB in a community or country. Moreover, the number of patients receiving treatment is small compared with the number of new and existing MDR TB cases. It is estimated that only 10 percent of new MDR TB cases are treated each year, and fewer than 2 percent of patients are receiving verifiable, quality-assured second-line anti-TB drugs. Cassell stressed that, among the small population of patients receiving treatment, many are not receiving drugs that actually address their drug resistance profile, and therefore their treatment is ineffective.

Cassell cited several themes that emerged from the presentations and discussions at the 2008 and 2010 workshops in Washington, DC, and Pretoria, South Africa, respectively:

- Primary infection, or human-to-human transmission, is more common than many experts previously thought.
- The development and implementation of a point-of-care diagnostic test would speed the effective diagnosis of patients and permit initiation of treatment as soon as possible. Such an innovation could reduce the period of a patient's infectivity, protecting others in the community, and speed delivery of the appropriate care regimen.
- Bottlenecks in the procurement and distribution of high-quality drugs are a major barrier to effective treatment of patients.
- Development of a "cocktail" of three to four new TB drugs is warranted to treat the variety of drug-resistant strains that are emerging, as well as cases that are considered to be untreatable with existing drugs.
- Technical, regulatory, and financial challenges to the successful development of multiple new TB drugs include

—*A high failure rate in the drug development process*—There is a 90 percent failure rate from the time a drug target is identified to the time a drug achieves regulatory approval.
—*Lengthy time line*—The average time from discovery of a new drug to its approval is 10–14 years.
—*High financial cost*—The average cost of bringing a single drug to market is $1 billion, whereas the total global investment in TB drug development was $179 million in 2009.

Cassell closed by emphasizing her view that failure to acknowledge the new realities of drug-resistant TB and to act rapidly will be catastrophic for many countries and will greatly jeopardize the public health globally. She urged the scientific and medical communities to communicate the new realities of drug-resistant TB to the public and to policy makers, who must translate the data into policies that appropriately reflect the magnitude and urgency of the problem.

ORGANIZATION OF THE REPORT

This report summarizes the main points made at the workshop during both the formal presentations and the discussions among participants. Observations and recommendations made at the workshop do not represent the formal positions of the IOM or RAMS; however, they have provided valuable input to the Forum on Drug Discovery, Development, and Translation and to the IOM as both bodies deliberate on future initiatives.

Presentations at the workshop addressed the following topics:

- a global overview of TB and its growing drug resistance, as well as epidemiological data on drug-resistant TB from two other high-burden countries, South Africa and China (Chapter 2);
- the history of TB control and management in Russia and the epidemiology of drug-resistant TB in the country today (Chapter 3);
- TB transmission and infection control, both in particular countries and in specific settings, such as hospitals (Chapter 4);
- the development of new methods for diagnosing drug-resistant TB in patients, as well as the need for improved laboratory capacity (Chapter 5);
- treatment of drug-resistant TB, including TB and HIV coinfection and innovative research on MDR TB treatment (Chapter 6);
- the incidence and treatment of MDR TB in vulnerable populations, including children, substance abusers, and the incarcerated (Chapter 7);

- the second-line drug supply chain for treatment of MDR TB (Chapter 8); and
- the development of new TB diagnostics and drugs (Chapter 9).

Each of these chapters opens with a box listing the key messages emerging from the workshop presentations and discussions, as identified by the workshop rapporteurs. Finally, Chapter 10 looks back at the major viewpoints expressed at the workshop and looks forward to next steps suggested by workshop participants.

2

A Global Perspective on Drug-Resistant Tuberculosis

Key Messages

- Despite considerable progress against drug-resistant TB in many countries, great challenges remain in the areas of infection control, diagnostics, treatment, and drug development.
- Unless these challenges are met, the numbers of cases and levels of drug resistance will continue to rise.
- The battle against drug-resistant TB can be viewed from a social medicine perspective, in which social and biomedical factors are intertwined.

Salmaan Keshavjee, Harvard Medical School, Partners In Health, and chair of WHO's Green Light Committee (GLC), explained that MDR TB occurs in most countries of the world. In parts of Europe and Asia, rates of MDR TB among new TB cases from 1994 through 2009 were less than 6 percent. In parts of Eastern Europe and Russia, however, this figure was more than 18 percent. In many parts of the world, 12–30 percent of patients being retreated for TB have MDR TB. In some parts of Eastern Europe and Central Asia, MDR TB represents more than 50 percent of retreatment cases.

Keshavjee shared 2008 data from WHO indicating that among 27 high-burden countries, China, India, and Russia have the highest numbers

of MDR TB patients. It is estimated that 50 percent of MDR TB cases worldwide occur in China and India. Other countries with large numbers of MDR TB cases include Bangladesh, Indonesia, Myanmar, Nigeria, Pakistan, the Philippines, and South Africa.

This chapter begins by briefly reviewing the difficulties involved in estimating the burden of MDR TB. It then looks at MDR and XDR TB first in South Africa and then in China. The fourth section presents an historical perspective on MDR TB control efforts. The final section details remaining challenges in global efforts to combat MDR TB.

DIFFICULTIES IN ESTIMATING THE BURDEN OF MDR TB[1]

The official figures for MDR TB prevalence and incidence raise many questions. Farmer cited official numbers of 1.5 million cases of MDR TB, with 500,000 new cases annually. But he raised the question of how prevalence could remain at 1.5 million with 500,000 new cases annually given existing rates of mortality and transmission.

Farmer acknowledged that estimating the prevalence and incidence of diseases such as TB is extremely complicated. In Lesotho and Peru, for example, similar conditions exist. They include poor health care infrastructures, limited access to diagnostics, fragmented health care delivery systems, a lack of public support for TB care, varying levels of knowledge about TB among providers, inadequate infection control, and a shortage of appropriate drugs for circulating strains. However, the importance of these factors differs considerably between the two countries. In Lesotho, for example, transnational migration is a significant part of the problem, but it is much less important in Peru. These differences make modeling and quantification difficult. Farmer quoted the French poet Paul Valéry: "All that is simple is false, and all that is complex is useless."

Farmer noted that modeling is a good way to estimate the size of a problem. It may be the case, as some have insisted, that half of TB cases are not diagnosed at all and that the number of drug-resistant TB cases is unknown. But important progress has been made in the past decade. XDR TB is recognized as a serious health issue. Molecular diagnostics have created a much deeper understanding of the resistance problem. According to Farmer, it will be especially useful to link a social medicine perspective on the disease with new molecular techniques to better appreciate the dimensions of the epidemic, as well as the directions in which it is headed (see Box 2-1).

[1]This section is based on the presentation of Dr. Farmer.

BOX 2-1
A Social Medicine Perspective[a]

Farmer suggested that a social medicine perspective is the best way to think about TB, whether considering new diagnostics, new therapeutics, or programs to prevent and respond to drug-resistant TB. This social medicine perspective is deeply rooted in Russia, where social vulnerability is a leading cofactor for TB. For example, rates of TB are much higher among the unemployed than the employed in Russia, in the United States, and throughout the world.

Drug resistance is also a social medicine problem. Just a few weeks after the introduction of streptomycin to combat TB in the 1940s, patients began to develop resistance to the drug. TB specialists sometimes forget a general rule of infectious disease—when pathogens are challenged with anti-infectives, they mutate and develop resistance. Farmer noted that this is a classic social medicine problem in infectious disease. The development of drug resistance is a natural cycle, although modern medicine can break this cycle by introducing new diagnostics or therapeutics.

An integral part of a social medicine perspective is the understanding that help-seeking behaviors also have a profound influence on a disease like TB. Regardless of whether formal programs or national policies to treat MDR TB are in place, the sick and their family members seek care. Farmer said this help-seeking behavior is a powerful driver of antibiotic use, which in turn shapes drug resistance.

Uncontrollable natural forces also have a profound effect on population health and the ability to provide care. An obvious example comes from the devastation in Haiti that occurred early in 2010. When the Haitian earthquake leveled the entire capital city—with 20 percent of all federal employees in Haiti being killed—not just the physical but the human infrastructure was massively disrupted, said Farmer. For example, of the eight people from the United Nations on the leadership team in Haiti with which Farmer was working, seven were killed. Farmer said this has been a reminder, in a very crude way, of the fact that large-scale social forces that are completely beyond the control of physicians, epidemiologists, pharmaceutical manufacturers, and policy makers can shape, and reshape, the dimensions of a problem.

The collapse of the Soviet Union in the late 1980s similarly led to enormous disruptions in the provision of TB prevention and care. Interruptions in the supply chain of medications led to acquired resistance, and high rates of incarceration helped the disease spread. “In other words, large-scale social and political forces shaped the nature of the epidemic here, as elsewhere in the world,” said Farmer.

continued

BOX 2-1 Continued

Biosocially complex phenomena require multiple and complementary methodologies. A useful metaphor is to think of several spigots or faucets turned on at the same time. In the 1980s, drug resistance was thought to arise from inadequate treatment programs and from patients who failed to adhere to treatment regimens. According to Farmer, "It turns out that there are many more spigots turned on than we understood." Reinfection played a major role. Nosocomial transmission served to amplify the epidemic. Strain variation became a consideration. While the number of turned-on spigots is not infinite, Farmer said, there are at least four or five major factors that vary from place to place. The bottom line is that drug-resistant TB is an exceedingly complex disease that will require more than simple models.

The TB community has several immutable responsibilities, Farmer said:

- It must work on novel tools for prevention, diagnosis, and care. Most of these tools will come from basic science.
- It must avoid trade-offs between prevention and care, which in turn reflect trade-offs between public health and clinical medicine. "Those trade-offs have been very palpable and pernicious," he said, especially in places where resources are scarce. On a positive note, new diagnostics are being linked more rapidly to implementation, and many more people now understand that proper diagnosis and treatment are central to prevention. This represents important progress. In Russia, in particular, prevention and care have been integrated for many decades.
- It must work from a biosocial framework, whether the subject is basic science or TB control. In particular, MDR and XDR TB can be properly understood only from this broad biosocial view.
- The flow from several spigots can be stopped at the same time. Infection control is linked to ventilation, to administrative controls, and to the quality of diagnosis and care. Diagnostic methods are linked to both care and prevention. For example, a molecular diagnostic for rifampin resistance would be invaluable, since one mutation describes about 80 percent of rifampin resistance, and

rifampin resistance stands as a marker for MDR TB. Yet such a diagnostic is not yet available,[b] although Farmer commended the Russian TB community for working hard to improve the quality of diagnostics. "We need new preventives, we need a vaccine, we need new diagnostics, we need new therapeutics, and we also need to focus on the implementation gap and get these out into the field," Farmer said. New discoveries and technologies will be essential to counter increasingly resistant TB. New drugs now in development pipelines were not even imagined several years ago. Also, a paradigm shift in diagnostics is about to occur with the advent of molecular techniques. These advances could be a large part of the solution to the problem.

Clinical trials cannot be conducted ethically without a commitment to improving the scope, scale, and quality of clinical efforts, Farmer said. There needs to be a unified, aspirational standard of care, not the cheap comfort of alternative therapies for people from different backgrounds or different regions. The clinical imperative must always be transregional and transnational, even though most regulatory bodies and review boards are either institutional or national. That is why international workshops and other meetings are so important, according to Farmer, even though "transnational" is a term not used frequently in clinical medicine. This tension between the local and the translocal, or between the small-scale and the large-scale, is inevitable, Farmer said, especially when dealing with an airborne communicable disease. Farmer stated that he has a deep faith in the ability of science to help us develop the tools we need.

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[a]This box is based on the presentation of Dr. Farmer.

[b]Since the workshop was held, a new, fully automated DNA test (Xpert MTB/RIF) for TB has been validated and subsequently recommended by WHO for broad implementation as the initial diagnostic for individuals suspected of MDR TB or HIV–TB coinfection. The test simultaneously detects TB and rifampicin drug resistance (a reliable indicator for MDR TB) in sputum. WHO reports that the Foundation for Innovative New Diagnostics (FIND) has negotiated a reduced price for 116 low- and middle-income countries (including South Africa, Russia, India, and China) of US$16.86 per test cartridge. The test provides results in 100 minutes, allowing proper treatment to begin immediately (WHO, 2010d).

MDR AND XDR TB IN SOUTH AFRICA[2]

Coetzee reported that the incidence of TB in South Africa is 600 cases per 100,000 population and in two of the country's provinces, the incidence is well over 1,000 per 100,000 population. At the same time, the prevalence of HIV coinfection in TB patients is about 60 percent.

In 2007, South Africa had the fourth-highest reported total number of MDR TB cases among nations. In 2009 the total exceeded 9,000 patients, which is a large number for a country with 48 million people. At the same time, the percentage of MDR TB cases among new TB patients remains below 5 percent. South Africa also has a significant XDR TB burden, accounting for 7–8 percent of MDR TB cases. These numbers are not exact, said Coetzee, because some provinces are grossly underserviced, making it impossible to draw firm conclusions about numbers of cases.

MDR AND XDR TB IN CHINA[3]

China is a very large country with a population of more than 1.3 billion. It consists of 31 provinces and the Xinjiang construction corps, along with two special administrative regions—Hong Kong and Macao. Chen described the country's strategies for MDR TB control and prevention. According to a national TB prevalence survey conducted in 2000, China had about 4.5 million TB patients; about 1.5 million new cases occurred that year and 130,000 deaths from TB. According to Chen, more recent data indicate that China has more than 1.3 million new cases of TB each year, representing the world's second-largest TB burden.

The estimated incidence of MDR TB is about 120,000 annually, and the estimated incidence of smear sputum–positive MDR TB is about 80,000—again the second-largest burden among the 27 MDR TB high-burden countries. Box 2-2 presents the results of a national drug resistance surveillance conducted in China in 2007–2008.

As noted in Chapter 1, patients with MDR TB need longer and more complex treatments than those with drug-susceptible TB. Since at least four second-line drugs are required, MDR TB patients experience more serious adverse drug reactions, and expenditures for these patients can be 100 times greater or more than those for drug-susceptible cases. In the 16 provinces of China where the Global Fund to Fight AIDS, TB, and Malaria is supporting the treatment and management of drug-resistant TB patients, the total budget is about $78 million.

[2]This section is based on the presentation of Gerrit Coetzee, National Health Laboratory Service of South Africa.

[3]This section is based on the presentation of Mingting Chen, National Centre of Tuberculosis Control and Prevention of China.

China has encountered success in controlling and preventing TB, said Chen. The Directly Observed Therapy, Short course (DOTS) coverage rate is 100 percent, the detection rate of new cases is about 80 percent, and the cure rate for new cases is more than 90 percent. China achieved the targets set by the country's National Tuberculosis Plain and cured 3.1 million patients from 2001 to 2007.

To combat MDR and XDR TB, China is enhancing the quality of DOTS through several steps:

- making a strong government commitment;
- improving the laboratory network;
- identifying TB patients in vulnerable groups and giving them more care;
- improving the recording and reporting system for TB;
- improving the quality of drugs, including first-line and second-line drugs;
- implementing improved practices in drug supply and management systems; and
- emphasizing cooperation between public health institutes and hospitals.

China also is formulating a national policy and launching pilot projects for the programmatic management of drug-resistant TB. It is increasing the number of pilot sites for implementing drug resistance surveillance and is improving laboratories from the national to the county level to meet the standards for MDR TB diagnostic tests (see Box 2-2 for a discussion of China's drug-resistant TB surveillance results).

For the treatment and management of MDR and XDR TB patients, China is taking steps in the areas of technical support, research, drug resistance surveillance, diagnosis, and cooperation. In the area of technical support, it is developing:

- guidelines for the programmatic management of MDR TB;
- a manual for second-line drug management;
- guidelines for TB infection control;
- guidelines for responding to adverse drug reactions; and
- a manual for drug susceptibility testing for laboratories.

In the area of research, China is:

- conducting a survey of policies against MDR and XDR TB;

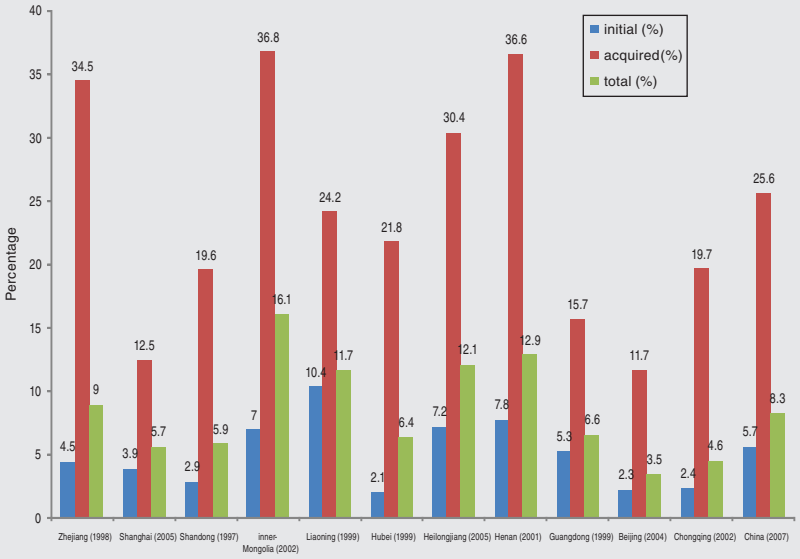
BOX 2-2
Drug-Resistant TB in China: Surveillance Results[a]

Renzhong Li of the Center for Disease Control and Prevention, China, reported that China has been engaged in an effort to establish a surveillance system for resistance to anti-TB drugs according to guidelines from WHO and the International Union Against Tuberculosis and Lung Disease. The goals have been to collect data on initial and acquired drug resistance in 11 provinces initially and then for the whole country, to determine the prevalence of drug-resistant TB at the provincial and national levels, and to evaluate the efficacy of ongoing TB control strategies.

During the national drug resistance surveillance in 2007–2008, 70 counties in all 31 provinces of China were randomly selected for surveillance by cluster sampling. Sputum smears and cultures were examined at the county level, while drug susceptibility tests were performed at the national level. Bacterial typing and susceptibility testing were done for all positive samples. The patient's history was carefully obtained, and available medical records were reviewed to determine whether the patient had previously received anti-TB drugs. All laboratory processes were quality assured in cooperation with the Hong Kong Supranational Reference Laboratory.

In the national drug resistance survey, MDR TB cases were found to be 8.3 percent of all cases. Among new cases, 5.7 percent were MDR TB, and the MDR TB rate among retreatment cases was 25.6 percent. The proportion of XDR TB cases was 0.7 percent among all cases, 0.5 percent among new cases, and 2.1 percent among retreatment cases.

Of the 11 provinces where surveillance has been conducted to date, Inner Mongolia has shown the highest percentage of MDR TB cases, at 16.1 percent (see the figure below). Among new cases of TB, the resistance rate is 7.0 percent, while resistance is found in 36.8 percent of retreatment cases.



Percentages of MDR TB among initial (new) and retreatment (acquired) cases differ among 11 surveyed provinces and in comparison with China as a nation (last bar graph on right). SOURCE: Li, 2010.

The proportion of resistance to isoniazid (19 percent) or streptomycin (28.9 percent) among all cases is higher than for other drugs. The proportions of resistance to streptomycin, ethambutol, ofloxacin, and kanamycin among MDR TB cases are 73 percent, 55 percent, 27 percent, and 12.5 percent, respectively. MDR and XDR TB prevalence is higher in rural and developing areas than in developed areas.

[a] The information presented this box is based on the work of Renzhong Li, Lixia Wang, Mingting Chen, Yanlin Zhao, Caihong Xu, and Cheng Chen of the National Center for Tuberculosis Control and Prevention, Center for Disease Control and Prevention, China.

- using a mathematical model to analyze the cost-effectiveness of programmatic management of drug-resistant TB over the next decade; and
- providing other forms of evidence on programmatic management of drug-resistant TB for policy makers.

In the areas of drug resistance surveillance and diagnosis, China is:

- updating the epidemiology of drug-resistant TB;
- conducting drug resistance surveillance in 13 provinces with support from WHO, in 6 provinces with support from the Global Fund, and in 1 province with support from local government;
- accelerating the implementation of rapid diagnostic methods; and
- assessing rapid diagnostic methods for MDR TB.

Finally, in the area of cooperation, China is determining effective models of cooperation between hospitals and TB dispensaries. The responsibilities of hospitals, according to Chen, include diagnosis, treatment, and response to side effects, whereas the responsibilities of public health institutes include management, supervision, follow-up, detection, and drug management.

The next step is to carry out the National Action Plan on Programmatic Management of Drug-Resistant TB in China. The pilot phase of 2007–2009 is currently undergoing preliminary scale-up, with rapid scale-up scheduled for 2013–2019 and full coverage for 2020 and beyond. During the rapid scale-up, all smear-positive TB cases will be tested using the Hain test. This plan will require regulation and legislation, an MDR TB expert committee at the central level, a high-quality and continuous supply of second-line anti-TB drugs, cooperation, and fund-raising mechanisms.

Already a single stream of funding from the Global Fund has been received, and 87 prefecture levels in 29 provinces will be covered. Actions expected in the future include expert review and demonstration, issuance of an action plan by the State Council of China, and integration of the action plan for MDR TB control with the National TB Control Plan for the next 10 years (Chen, 2010).

The Bill and Melinda Gates Foundation is supporting a project to develop new models, tools, and techniques for preventing and controlling MDR and XDR TB in China. Launched on April 1, 2009, the project covers four prefectures in four provinces in Phase I and will expand to 20 prefectures in six provinces in Phase II. Project activities include:

- determining a model and mechanism for cooperation between hospitals and public health institutes;

- developing policies, guidelines, and operational procedures for this cooperative program;
- determining the financing and incentives needed to implement the program;
- providing an uninterrupted supply of quality second-line TB drugs;
- implementing collaborative models;
- evaluating the model program; and
- developing human resources needed to implement and scale up the cooperative model.

The program is designed to provide a good model for the control and prevention of MDR TB, a standardized regimen for treatment, management of second-line drugs, laboratory methods for detection, the development of human resources, and a strong government commitment to the program goals. MDR TB treatment and management sites have been set up by prefecture, with plans for gradual and capacity-based expansion. Also, the TB dispensaries and other health services have been directed to cooperate closely.

Chen pointed out several lessons learned from both successful and unsuccessful experiences in the effort to fight drug-resistant TB in China. First, it is necessary to establish policies to regulate the management of MDR TB and the use of second-line drugs. Second, MDR TB control needs to be combined with broader changes in the medical system so the effort can draw on the resources of township health insurance plans, the new rural cooperative plans, the central government, and international cooperation. Third, depending on resources, an appropriate strategy for case finding is to give high-risk populations the highest priority and to screen all smear-positive patients for MDR TB. Fourth, the diagnosis of MDR TB cases can be accomplished more rapidly by using molecular biology methods. Finally, it is important to increase the number of TB staff at all levels and to enhance human resources through training.

HISTORICAL PERSPECTIVE ON MDR TB CONTROL EFFORTS[4]

Keshavjee explained that when New York City experienced an outbreak of drug-resistant TB in the late 1980s and early 1990s (see Box 2-3), it quickly became clear that these patients needed appropriate diagnostics, particular drug regimens, and a system of treatment follow-up in order to be cured. As a result, by the time the first global drug resistance surveys began in the mid-1990s, treatment regimens were well defined and relied on drugs that had been tested in the 1950s and 1960s. In Russia, too, the

[4]This section is based on the presentation of Dr. Keshavjee.

BOX 2-3[a]
The New York City TB Epidemic

In 1991, Hamburg became health commissioner of New York City just as the city was experiencing an epidemic of resurgent TB. Nearly 4,000 cases were reported that year, representing a 152 percent increase over 1980. "This was sadly ironic," said Hamburg, "because when I was in medical school I had learned about TB as a disease of historical interest only, not an ongoing scourge. I certainly never imagined that I would be spending so much of my time in New York City dealing with the problem of tuberculosis."

Having had limited previous experience with TB, Hamburg was "stunned" to learn that this was not a new problem. TB rates had been increasing for years, particularly in inner-city areas and underserved communities. The problem was fueled by poverty, homelessness, AIDS and other diseases, and the erosion of the public health infrastructure. In addition, at that time New York City was experiencing an economic crisis, although not on the scale seen today. "Every year the TB program had been noting increases, raising signals of concern, but we had failed to act," said Hamburg.

New York City quickly mobilized to mount a comprehensive response. Officials invested significant energy and resources in ensuring appropriate treatment. The implementation of DOTS increased the number of patients receiving directly observed therapy from 100 in 1988 to 1,300 in 1993. The city also increased screening, monitoring, and isolation capacity in hospitals, shelters, and other congregate facilities. Thanks to a well-designed program, adequate resources, and what Hamburg described as "real political will and program commitment from the mayor and others," New York City was able to turn the epidemic around. Between 1992 and 1997, the number of TB cases in the city dropped by almost 46 percent, and for the most drug-resistant cases, by 86 percent. "Frankly, we were surprised by how quickly we were able to make that kind of difference," said Hamburg. "It was a real accomplishment. I'm very proud of what we did and how the city responded overall to the epidemic. We were fortunate. We had resources. We had leadership. I think we showed what could be done."

[a]The information presented in this box is based on the presentation of Margaret Hamburg, commissioner, U.S. Food and Drug Administration.

treatment of drug-resistant TB during this period relied largely on previously developed approaches.

However, there was some reluctance on the part of WHO to apply the same approaches in less developed countries, said Keshavjee. In its publication *Groups at Risk* (WHO, 1996), WHO suggested that "MDR TB is too expensive to treat in poor countries; it detracts attention and resources from treating drug-susceptible disease." As a result, poorer countries were urged to ignore the treatment of MDR TB with second-line anti-TB drugs and to focus on the DOTS strategy (using first-line short-course chemotherapy) as a means of enrolling large numbers of patients in TB treatment. According to Keshavjee, WHO's position exemplifies a policy decision based on a discourse that did not fully reflect the available scientific data. In response to WHO's stance, some groups took up the challenge of proving that MDR TB could be treated successfully in resource-limited settings.

In August 1996, Partners In Health and Harvard Medical School, with the Peruvian National TB Program, initiated a large-scale, community-based program to combat drug-resistant TB in the Northern Cone of Lima—the first program of its kind in any poor country. The challenge was substantial, Keshavjee noted, as their efforts were counter to the global discourse regarding the appropriate approach to treating drug-resistant TB in disadvantaged populations. Employing a treatment and transmission control strategy similar to that which had been used in New York City, the efforts in Peru were successful and achieved an 83 percent cure rate (PIH, 2010).

Based in part on the success in Peru, Partners In Health and other groups developed their own guidelines for the medical management of drug-resistant TB. Several philanthropists funded care for patients with MDR TB. In addition, a series of meetings starting in 1998 focused on the treatment of drug-resistant TB, leading to the development of DOTS-Plus, a supplemental approach to DOTS designed to cure MDR TB using second-line drugs. This was followed later by the formation of a coalition of partners that included the U.S. Centers for Disease Control and Prevention (CDC), the Task Force for Child Survival and Development, and WHO. In 2000, a coalition of nongovernmental, governmental, and multilateral partners created the GLC, with the objectives of ensuring access to quality-assured second-line drugs at affordable prices, monitoring and evaluating second-line drug use in approved projects, and promoting technical assistance for MDR TB projects to ensure that they would adhere to WHO guidelines.

Once the GLC was formed, several DOTS-Plus pilot projects—including those in Lima (Peru), Tomsk (Russia), Manila (Philippines), Latvia, and Estonia—joined and became models of care. Over the next few years, data from these projects informed what became guidelines for the programmatic

management of drug-resistant TB (WHO, 2006). Keshavjee noted that although there had been previous WHO guidelines, these new guidelines better reflected international standards of care.

A number of other treatment and funding initiatives also advanced the treatment of MDR TB. In 2002 the Global Fund Board decided that all MDR TB drugs funded by the Global Fund should go through the GLC mechanism to ensure the efficacy of the drugs. UNITAID was created in 2006 by France, Brazil, Norway, Britain, and other countries with the aim of lowering the market price and increasing the availability of drugs. Money became available from the U.S. Agency for International Development (USAID), the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), and the Lilly MDR TB Partnership to provide assistance to countries through the WHO and GLC systems. Combined with assistance from other partners, the result was a rapid increase in GLC projects in countries throughout the world. By 2009, roughly 60,000 patients were covered. Cure rates have averaged 62.8 percent, with a slight drop-off over time as the number of projects has increased.

REMAINING CHALLENGES[5]

Keshavjee stressed that, despite recent successes in mobilizing a number of international resources to fight MDR TB, significant challenges remain. As the urgency of treating the increasing number of MDR TB patients (diagnosed and undiagnosed) grows, the organizational and technical challenges involved in implementing the necessarily complex health interventions also grow. Challenges remain in the areas of infection control, diagnostics and laboratory infrastructure, second-line drug supplies, treatment delivery and health care infrastructure, and drug development. Failing to act on these challenges will have dire consequences, Keshavjee said.

Infection Control

Halting the person-to-person transmission of MDR TB is integral to any effective TB control program. Infection control measures are most commonly located in treatment facilities, which can be a nexus for the transmission of TB bacilli. A study from Tomsk, Siberia, showed that patients hospitalized for drug-susceptible TB had a sixfold greater risk of contracting MDR TB than those not hospitalized (Gelmanova et al., 2007). Part of the reason for this increased risk of infection is delays in diagnosis. Patients wait together for weeks in hospitals, many of which lack proper infection control, to learn whether they have MDR TB.

[5]This section is based on the presentation of Dr. Keshavjee.

A number of interventions are possible even in resource-limited settings. In Lesotho, for example, infection control measures include respirators worn by staff and TB wards with negative pressure ventilation. The design of infection control measures can vary according to the unique needs and capabilities of the community. For instance, the climate in some parts of Africa lends itself to doors and corridors that open to the outside, whereas in Tomsk, the cold climate necessitates internal ventilation systems.

Diagnostics and Laboratory Infrastructure

In the area of diagnosis, rapid culture and drug sensitivity testing for MDR TB is desperately needed. In parts of many countries, people cannot access clinics easily. Once they reach a clinic, solid culture tests can take 4 to 8 weeks, liquid culture tests 2 to 4 weeks, and rapid molecular tests 2 hours to 2 days; many of these tests require proper laboratory infrastructure (see Chapter 5 for more information on current diagnostic methods). Returning for the test results and the initiation of treatment can be difficult for patients. If testing were available at the point of care, treatment could start right away, which in turn would reduce transmission to other patients.

Important steps have been taken in this area in the past 10 years. Laboratory facilities have been built in a number of resource-poor settings. In 2006, for example, Partners In Health worked with FIND to establish a state-of-the-art laboratory facility in Lesotho for approximately $500,000. In the span of about 6 months, Lesotho went from not having proper laboratory facilities to having solid media culture, then liquid media culture, and most recently DNA-based technologies. Today, Lesotho's laboratory can diagnose a patient's drug resistance profile in 2 days or less. This capability is especially important since the country has high levels of HIV, which increases the risk of contracting TB, the risk of having a drug-resistant form of TB, and the risk of experiencing excess morbidity and mortality (see Chapter 6). Thus, diagnosing patients quickly and initiating the appropriate regimen of TB drugs and HIV antiretrovirals is critical to optimal patient care.

The Global Laboratory Initiative (GLI), created by WHO and the STOP TB Partnership in 2007, draws extensively on the Lesotho model. It has received funding from UNITAID to implement this type of laboratory strategy in other countries, along with a supranational laboratory network to monitor new technologies. The goal is to be able to diagnose 130,000 people with these laboratories by 2013. This is an important step, said Keshavjee, but it will remain important to expand efforts to develop and rapidly deploy point-of-care testing for drug-susceptible and drug-resistant TB.

Responding to a question about the ideal diagnostic laboratory, Keshavjee said that the ideal test would use a sample from a patient's

mouth, produce results very quickly, determine whether the patient has TB, and identify the drug resistance pattern of the strain. If such a test could take place within 1–2 hours, people could wait for their results and be started on the appropriate treatment immediately. Today, when results can take up to 2 months to be available (depending on the technology at hand in a given setting), many patients cannot even be found once their results are available. Peter Cegielski of CDC agreed that a rapid molecular screen for resistance would permit individualized treatment. In the meantime, he suggested, suspected MDR TB cases should be treated aggressively with empiric regimens until their drug susceptibility test results become known, after which treatment can be individualized.

Second-Line Drug Supplies

The situation with respect to second-line drugs for treating MDR TB is characterized by an inadequate number of manufacturers of these drugs, a limited supply of quality-assured drugs, and insufficient forecasting of need that contributes to opaque markets for drug manufacturing. Second-line drugs also have seen serious delivery delays for various reasons. Under the current global system, countries are required to use a central procurement mechanism housed at the STOP TB Partnership; while this mechanism has helped many countries, it does not work for all. For example, some countries use a tender process whereby they must take bids to purchase drugs, while others may want to use local manufacturers, which makes buying quality-assured drugs from outside the country difficult.

WHO has a prequalification program to identify quality anti-TB drugs. The number of prequalified suppliers increased from two in 2007 to eight in 2009. Also, the Global Drug Facility (GDF) established a Strategic Rotating Stockpile of second-line drugs for 5,800 patients, developed a forecasting tool, and formed a price negotiation task force. But Keshavjee noted that these efforts will not fully meet the needs of even a significant fraction of the estimated 500,000 new MDR TB patients each year. He suggested that new ways of thinking about the provision of drugs are needed, as are new drugs beyond those already in clinical development for TB treatment.

Treatment Delivery and Health Care Infrastructure

The STOP TB Partnership developed a plan to treat 1.6 million people between 2006 and 2015. But with 500,000 new patients a year, this strategy leaves many people to seek alternative types of care that are not effective and can worsen the drug resistance problem, according to Keshavjee. Even the goal of reaching 1.6 million people has not been achieved. Treating MDR TB requires not only that people take the necessary drugs but also

that they do so for 2 years. Meanwhile, side effects must be monitored; laboratory services must be provided; and systems must be in place to transfer samples, provide results, analyze and manage data, and use information effectively to improve patient care. Many countries lack the funds, the health system capability, and in some cases the political will to carry out such a complex health intervention.

The GLC has approved treatments for approximately 60,000 patients over the past decade, and GLC-approved projects have actually treated about 23,000. However, the latter number represents less than 0.5 percent of the 5,000,000 new MDR TB patients over that 10-year period. In a given year, the GLC treats less than 3 percent of the estimated 500,000 new patients; countries have reported to WHO that they are treating around 8 percent of cases themselves. Thus, more than 85 percent of MDR TB patients either are not receiving any treatment or are obtaining some treatment of unknown duration or quality.

Many people with drug-resistant TB live in isolated communities, and expecting them to come to clinics for care every day or twice a day for 2 years is unrealistic. An alternative is to train local health care workers to administer injections. Community-based approaches also provide a way to treat large numbers of patients rapidly and safely, said Keshavjee. For example, MDR TB cases in Tomsk were increasing between 1998 and 2004 but then declined as efforts were made to provide universal access to treatment. Curing the reservoir of transmitting patients is important to lowering the incidence of both drug-resistant and drug-susceptible TB, Keshavjee observed. Ambulatory care also can be much less expensive than hospitalization, although most physicians are trained to think in terms of the latter.

In May 2009, the World Health Assembly adopted a resolution urging all member states to achieve universal access to diagnosis and treatment of MDR and XDR TB as part of the transition to universal health care coverage. The resolution calls for directly observed treatment and community-based and patient-centered care. Effecting these changes will require long-term technical assistance and, where necessary, on-site implementation teams.

The global community has not yet begun to treat drug-resistant TB as an emergency, Keshavjee stated. For example, the number of people receiving treatment through PEPFAR programs increased from 155,000 in 2004 to 1.64 million in 2008; however, there has been much less growth in the treatment of MDR TB. Moreover, individual countries need to move beyond relying on international sources of funding and take the initiative in expanding treatment. Peru, for example, shifted from a heavy reliance on Partners In Health and the Global Fund for MDR TB treatment in 2001 to a major reliance on government resources by 2006.

If the ideal MDR TB treatment delivery plan could be instituted and

were not limited by resources or political will, Keshavjee suggested, such a program would diagnose people rapidly, start them on the appropriate treatment immediately, and ensure that they remained on treatment. "Even in settings where we can diagnose people and we do bring them the drugs, it's very hard to keep them on [the treatment] for 2 years," he said. Also, new second-line drugs are needed to improve cure rates (see the next section and Chapter 8).

Cegielski suggested that the greater limitation in TB control is the human capacity to identify, manage, treat, and follow patients. The people who perform those roles must be adequately trained and motivated, which means they must be able to earn a reasonable living at what they do. "With unlimited funding, I would dramatically expand both training and compensation for the health care workforce," he said.

Finally, a participant stated that a key step in stopping the spread of MDR TB would be legislation forbidding free access to antibiotics without a prescription. In the former Soviet Union and China, essentially any drugs are available in drugstores. Cegielski observed that achieving the proper balance in antibiotic availability is difficult. Making antibiotics easily available has great benefits for people who suffer from infections other than TB. For example, he said he could not imagine restricting the fluoroquinolones to the treatment of TB because they are so widely useful for other infections. "There is not an easy solution," he said. "It's easy to say we need to control the second-line drugs, but we also have to look at the benefits that broad availability of antibiotics has had for populations."

Drug Development

The development of a new "cocktail" of three to four drugs to treat MDR TB is a scientific, organizational, and technical challenge that is key to advancing the treatment of drug-resistant TB, said Keshavjee. Antibiotics that are more effective, less expensive, and able to shorten the course of MDR TB treatment are greatly needed. Cassell noted that it takes 10–14 years and $1 billion to create a new drug from discovery to regulatory approval. Unfortunately, she said, the total global investment in the development of new TB drugs—$179 million in 2009—is lacking by current standards.

Consequences of Inaction

The consequences of inaction on the above challenges are dire, said Keshavjee. Over the next 10 years, 5 million new cases of MDR TB will occur if current incidence rates persist. If current mortality rates continue, more than a million people will die. The large pool of living, untreated

patients will continue to infect others. People will continue to buy drugs from pharmacies or receive drugs from relatives and take them for short periods, which will increase drug resistance. Current plans to treat these patients have major gaps. Already, many countries are reporting increasing levels of XDR TB, and the number of TDR TB cases is completely unknown. Despite notable successes in recent decades, the global community has thus far been unable to significantly reduce the burden of MDR TB throughout the world. Keshavjee suggested that a major transformation is necessary to have a meaningful impact on this growing epidemic.

3

Drug-Resistant Tuberculosis in the Russian Federation

Key Messages

- The breakdown of the Soviet Union exacerbated TB by increasing unemployment, poverty, migration, and social unrest, but the situation has been slowly improving over the past decade.
- On the other hand, the incidence of MDR TB has continued to increase, as has infection with HIV and coinfection with HIV and TB.

In Russia and the former Soviet Union, TB has been an acute problem.[1] Today, the official estimate of the incidence of TB is about 82 to 83 per 100,000 population. According to Perelman, not all cases are diagnosed, however, and not all patients are registered as incident cases; thus this estimate is an underestimation of the true burden of disease.[2] The estimate of 82 to 83 cases per 100,000 population also is an average that includes an incredibly diverse population and thus is not very revealing. Russia is a vast country, and the incidence of TB differs as much as tenfold among

[1]This introductory text and the following section are based on the presentation of Mikhail Perelman, Moscow Medical Academy.

[2]In Russia, estimated TB incidence (new and relapse cases) in 2009, including TB-HIV coinfection, was 106 per 100,000 population (confidence interval 89-125) (WHO, 2010c).

geographic regions. It is higher in the eastern portion of the country, with the highest rates in the Russian Far East adjacent to Mongolia, China, and Japan. Areas in that part of the country have an incidence ten times that of Moscow.

Before the breakdown of the Soviet Union, the prevention and treatment of TB were under stringent federal control. After the breakdown, many events occurred to exacerbate the problem of TB. Dislocations in the economy made the population poorer, and poverty is a risk factor for TB. Unemployment and crime rates worsened considerably, which encouraged the spread of TB in communities and the prison population. High levels of migration into the country also contributed to the spread of TB, as did military conflicts and the overall degradation of the health care system, which loosened previously stringent controls on the level of disease in the population.

Perelman explained that over the last decade, the TB situation in the Russian Federation has slowly improved. The number of new cases is somewhat lower, and both morbidity and mortality have been on the decline.

A HISTORICAL PERSPECTIVE

In 1943–1944, the Soviet Union received its first lot of penicillin, which was used by the military on the front lines. As early as 1944, the chief surgeon of the Red Army wrote about drug resistance after the potency of penicillin had declined substantially. When penicillin was recently reintroduced, however, it was much more effective, said Perelman.

Before drug therapy became available, TB was treated in Russia through surgery, which saved hundreds of thousands of lives. The surgery option also was used extensively in Scandinavia, France, and the United States, as described in journals such as the *Annals of Surgery*. Today, better diagnostic and surgical capabilities are available, such as surgery using state-of-the-art visual technologies. In Russia, from 12,000 to 14,000 surgical operations for TB are performed per year, and surgical treatment is about 85 percent effective. According to Perelman, however, the need for surgery is at least 25,000 cases, so the number of surgeries needs to double. In addition, surgery is complex and expensive and requires specialized departments and personnel who are aware of the TB problem.[3]

The proper approach to TB in Russia today, said Perelman, is for every person suspected of having TB to undergo a general medical checkup, including a chest examination. Russia did not accept DOTS

[3]In Russia, surgery is considered a component of treating patients with chronic TB that has been unresponsive to antimicrobial therapy, as well as newly diagnosed TB patients with complications, drug resistance, and/or intolerance to anti-TB drugs (Perelman, 2000).

in its initial version, and Perelman believes this was a good decision. If DOTS had been implemented, he suggested, the medical checkup would have been abandoned. Today about 50 percent of new cases in Russia are reviewed by x-ray, which provides good data with very little irradiation because digital systems are used. Also, treatment of patients under DOTS was supposed to be a short course. Perelman believes that patients left the program undertreated, and this short course was one of the reasons for the broad spread of MDR TB. Perelman stated that MDR TB also can result if treatment is discontinued based on sputum tests without consideration of cavities in lungs. Finally, he suggested that abandoning luminescent microscopy or treatment in sanatoriums would not have been appropriate in Russia.

An integrated approach to TB is important for prevention, said Perelman. If all people had a high standard of living and education on how to maintain their health, TB would be much less likely to spread. At present, complex combination treatment is needed and is most effective.

EPIDEMIOLOGY OF TB IN THE RUSSIAN FEDERATION[4]

Yakimova observed that TB remains a very serious problem in Russia. Approximately 320 new TB cases appear each day, and 64 deaths are associated with the disease.

The basic reasons for the TB epidemic in Russia are socioeconomic, medical, and biological, Yakimova stated. Socioeconomic causes include such factors as low living standards, unemployment, and migration. Medical causes include late detection, a lack of anti-TB therapy (especially second-line therapy), a shortage of laboratories, and insufficient infection control. Biological causes include the spread of MDR TB and HIV and the continuing adaptation of *M.tb.* to antibiotics.

International experts estimate that about 50,000 people in Russia have MDR TB. Between 40 and 70 percent of newly detected TB cases occur in socially vulnerable groups, including the homeless, the unemployed, migrants, and people with drug and alcohol dependencies (see Chapter 7). The incidence of TB among the unemployed is 750 per 100,000 unemployed people, compared with 45 per 100,000 employed people. Children from socially vulnerable groups contract TB 10 to 20 times more frequently than other children.

Altogether in Russia, 117,227 cases of TB were detected in 2009, which is equivalent to 82.6 per 100,000 population. This figure represents a decrease of 2.9 percent relative to 2008. The incidence among children

[4]This section is based on the presentation of Marina Yakimova, Central TB Research Institute, Russian Academy of Medical Sciences.

younger than 15 was 14.7 per 100,000, a decrease of 3.9 percent relative to 2008. The incidence among men is 2.8 times higher than that among women (Figure 3-1). Among all cases of TB in Russia, 12 percent occur in people incarcerated by the Ministry of Justice.

The incidence of TB grew markedly in Russia during the 1990s as the economy of the country deteriorated (Figure 3-2). As noted above, however, the incidence of the disease differs markedly across the country, with some Russian territories accounting for a disproportionate number of cases. Therefore, suggested Yakimova, a single approach will not be appropriate for all populations. TB incidence and mortality in Russia's prisons have fallen dramatically over the past 10 years, from 4,347 cases per 100,000 prisoners and detainees, with 238 deaths, in 1999 to 1,308 per 100,000 prisoners and detainees, with 80 deaths, in 2008. Detection and treatment also have lowered the percentages of people with TB in Russia who suffer the destructive pulmonary form of the disease.

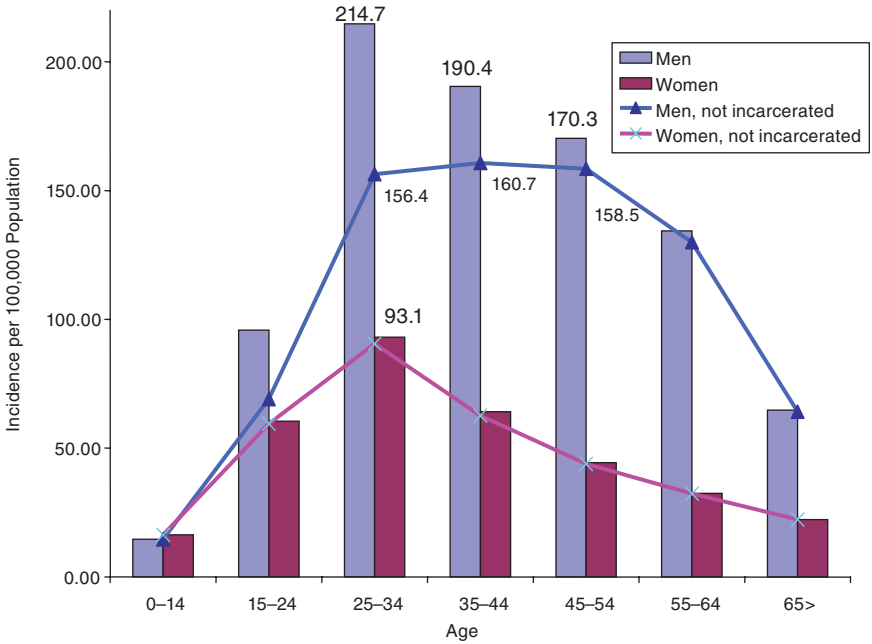


FIGURE 3-1 TB incidence by gender and age rises to a peak between ages 25 and 34.
SOURCE: Yakimova, 2010.

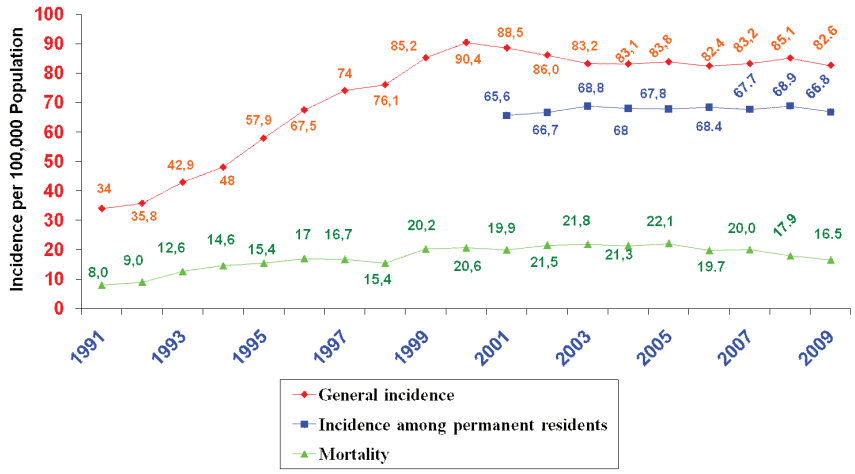


FIGURE 3-2 TB incidence and mortality rose in the 1990s and have declined slightly since.
SOURCE: Yakimova, 2010.

The effectiveness of detection and diagnosis varies among regions within the Russian Federation. Estimated detection rates are below 50 percent overall—"lower than we would like," said Yakimova. In some regions of the Russian Federation, many cases of TB go undetected. Detection is important because it determines the reservoir of patients who can serve as a source of infection for the general population.

Nevertheless, TB mortality has decreased in the past 5 years in the Russian Federation, as has the proportion of TB cases detected after the subject's death. An emphasis on TB in national and regional health programs has contributed to this decrease, with a new TB early detection and prevention program starting in 2010. Preventive measures, including infection control and vaccination or prophylactic chemotherapy, must be clearly designed and organized, Yakimova stated. The identification and treatment of TB cases, particularly for people with infectious forms of the disease, are critical to prevention. Other steps Yakimova recommended are:

- creating an integrated system for delivering TB health care, focusing on prevention and early diagnosis;
- designing and implementing initiatives to encourage TB testing among vulnerable groups;

- increasing the vigilance of general practitioners, family doctors, and specialists offering outpatient care;
- implementing directly observed therapy at all stages of TB health care;
- designing and implementing uniform treatment and diagnostic standards in TB health care;
- making improvements in diagnostic methods, combination therapy regimens, and rehabilitation (medical, social, and psychological);
- expanding facilities that offer an alternative to inpatient treatment, such as outpatient, day patient, and home care;
- providing training and retraining for specialists offering prophylactic, therapeutic, and diagnostic services to TB patients as continuing education;
- improving the physical condition and technology of medical facilities offering TB care and equipping them with modern medical and diagnostic equipment;
- guaranteeing the availability of good-quality first- and second-line therapies; and
- increasing the effectiveness of TB prevention initiatives (such as decontamination) in TB centers.

NATIONAL MDR TB SURVEILLANCE SYSTEM[5]

Full reporting of MDR TB has been ongoing in the Russian Federation since 1999, said Skachkova. This period has seen the gradual development of recording and reporting, epidemiological analysis and research, cohort analysis, legislation, and training. The last annual review of surveillance data was in 2008.

The recording of MDR TB underwent a change at the beginning of 2010. More detailed case records were instituted, and experts were tasked to review data and ensure accuracy. Laboratory documents also were collected and reviewed by the Ministry of Health. New forms are being introduced for recording MDR TB and the effectiveness of MDR TB treatment. Furthermore, a new project is being implemented for continuous tracking of TB patients and risk groups. These changes have enabled much more precise and accurate reporting of not only MDR but also XDR TB cases.

An assessment of MDR TB data that began last year has made it possible to calculate the primary incidence and prevalence of pulmonary MDR TB. Review of these data in turn makes it possible to evaluate the success rates for MDR TB treatment. The guidelines are that a minimum of 85

[5]This section is based on the presentation of Elena Skachkova, Central Research Institute for the Organization and Informatization of Health Care, Russian Federation.

TABLE 3-1 MDR TB Data from the Russian Federation, 2007–2009

	2007	2008	2009
Newly detected cases of culture-positive pulmonary TB	35,449	35,573	36,679
Relapse cases of culture-positive pulmonary TB	5,820	6,224	6,159
Newly detected cases investigated for drug susceptibility	31,560	34,241	33,540
Percentage of newly detected cases investigated for drug susceptibility	89%	91.1%	91.4%
Relapse cases investigated for drug susceptibility	5,151	5,489	5,554
Percentage of relapse cases investigated for drug susceptibility	88.5%	88.2%	90.2%
Resistance identified to any drug, newly detected patients	10,056 (31.9%)	11,365 (33.2%)	12,116 (36.1%)
Resistance identified to any drug, relapse cases	2,307 (44.8%)	2,757 (50.2%)	3,016 (54.3%)
MDR TB identified, newly detected cases	4,085 (12.9%)	4,656 (13.6%)	5,193 (15.5%)
MDR TB identified, relapse cases	1,280 (24.8%)	1,580 (28.8%)	1,869 (33.7%)

SOURCE: Skachkova, 2010.

percent of culture-positive patients should be investigated. Also, with effective TB prevention, widespread drug susceptibility testing, and widespread treatment, the incidence of pulmonary MDR TB should not exceed 1.5 per 100,000 population, and prevalence should not exceed 9 per 100,000.

More than 90 percent of newly detected culture-positive TB cases are now investigated for drug susceptibility in the Russian Federation (Table 3-1). The percentage of newly detected cases with resistance to any drug has increased in recent years, to 36 percent in 2009, while the resistance to any drug among relapsed cases rose to 54 percent in 2009. MDR TB was identified in 15.5 percent of newly detected cases and in 33.7 percent of relapse cases.

Together, these trends point to an increase in the number of MDR TB cases over the past decade (Figure 3-3). This increase is related to the expansion of drug susceptibility testing and to improved investigation of drug-resistant TB. It is also due in part to an increase in the number of unsuccessfully treated patients and to a lack of directly observed treatment.

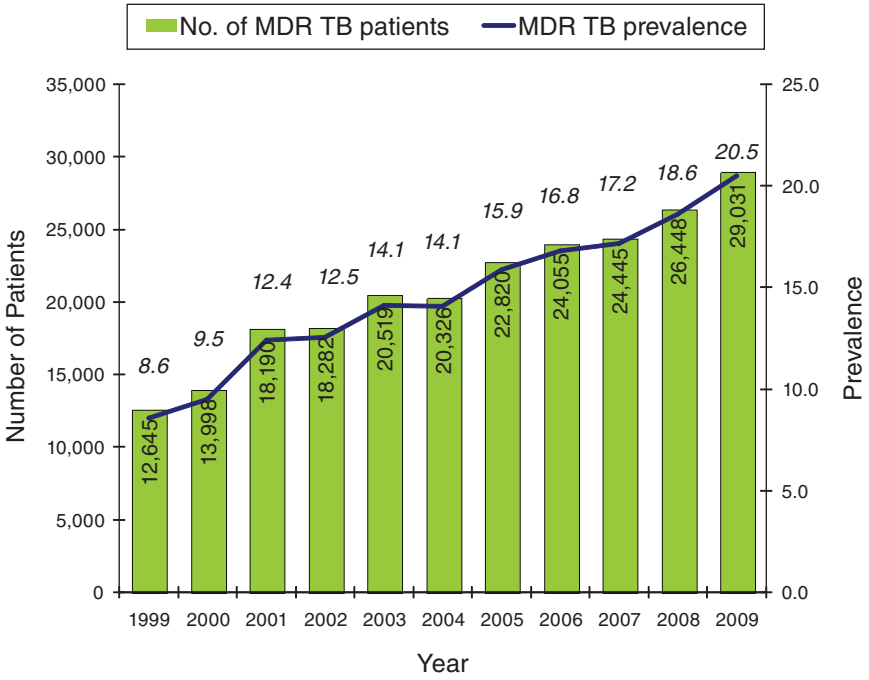


FIGURE 3-3 The number of MDR TB patients has continued to grow in the Russian Federation during the 21st century.
SOURCE: Skachkova, 2010.

Today a culture exam is performed in 97 percent of all patients. However, questions remain about the completeness and reliability of the resulting data since not all of the patients have positive culture results, and the quality of the samples is not 100 percent reliable.

Data from some parts of the Russian Federation also are not very reliable, according to Skachkova, especially where laboratory capacity is lacking. As this capacity is increased, incidence rates will increase as well. And with an overall incidence of MDR TB of 4 per 100,000 population, the rate of new cases remains significantly higher than the national goal of 1.5 per 100,000 population.

4

Transmission and Infection Control of Drug-Resistant TB

Key Messages

- Studies have found that more than half of new cases of MDR TB are among people never before treated for TB, pointing to the importance of transmission.
- Even many patients previously treated for TB acquire MDR TB through transmission rather than the evolution of resistance in an ongoing infection.
- There appears to be less transmission of XDR TB, although some clusters of XDR TB point to episodes of transmission.
- Prompt and effective treatment stops transmission, even among patients who remain smear positive.
- Systemic and long-term infection control measures within hospitals, including use of ventilators, bactericidal lamps, and mechanical ventilation, could be useful in reducing nosocomial transmission.

In addressing transmission and infection control, speakers presented case studies of China and South Africa. A third presentation examined the issue of reducing nosocomial transmission of drug-resistant TB.

TRANSMISSION OF DRUG-RESISTANT TB IN CHINA[1]

Among the approximately 1.3 million new cases of TB in China each year, 35.2 percent are drug-resistant, 5.7 percent are MDR TB, and about 0.5 percent are XDR TB, according to a 2007–2008 nationwide survey. The most important question to ask about this drug resistance, said Gao, is where it came from. Was it primary, in that a drug-resistant strain was transmitted from one person to another? Or was it acquired, in that a strain developed drug resistance during treatment because of noncompliance with a treatment regimen, poor-quality drugs, or treatment with a single drug? The significance of the distinction is that primary drug resistance indicates a need for better TB control to interrupt transmission, whereas acquired drug resistance indicates a need for better patient management to prevent the evolution of resistance.

A simple way to make this distinction is by referring to the history of care. If a patient has not been treated before, drug resistance is often assumed to be primary and the result of transmission. If a patient has been treated previously, drug resistance is often assumed to be acquired. WHO data indicate that 6–10 percent of new TB cases and 13–60 percent of cases in previously treated patients are MDR. One possible conclusion that could be drawn from these data, said Gao, is that previously treated patients should be the focus of improved patient care. In most parts of the world, however, new cases make up more than half of MDR TB incidence. In Shanghai, for example, from 2002 to 2006, 59 percent of the MDR TB cases were among new TB patients, indicating the transmission of drug resistance. The same observation can be made for XDR TB patients, although the total numbers are much smaller. In Shanghai from 2004 to 2007, 6 of 11 XDR TB patients represented new cases.

Another way to track transmission is by genotyping different strains. If two people have strains with the same genotype, transmission can be assumed. A search of the biomedical literature reveals several cases in which drug-resistant strains were responsible for clusters of MDR and XDR TB. In a 2009 study conducted in Samara, Russia, for example, 63 of 189 patients with XDR TB fell into two large clusters of similar genotypes. Gao observed that this means one of the patients could transmit, on average, to 31 or 32 patients.

In an ongoing study in China's Shandong, Shanghai, and Sichuan provinces, Gao and his colleagues found different clustering rates (i.e., clusters of TB with similar genotypes) in different geographic areas. According to preliminary results, 39 percent of TB patients in Shandong Province fell into clusters of similar genotypes, indicating primary transmission from

[1]This section is based on the presentation of Qian Gao, Fudan University.

one person to another. In the other two provinces, Shanghai and Sichuan, the rates at which clusters of patients with TB had similar genotypes were 10.8 and 13.2 percent.

Another study in which Gao was involved found that some previously treated patients were being reinfected by drug-resistant strains rather than developing drug resistance in ongoing infections. The researchers genotyped TB strains of 32 TB patients sampled before and after treatment. If the bacterial genotype changed, the drug resistance likely arose from reinfection; if patients had a mix of genotypes in an isolate, they had multiple infections. The results indicated that a significant fraction of the treated patients had been reinfected with a more drug-resistant strain. Thus, even some of the patients in whom the evolution of drug resistance was assumed may have developed primary resistance through reinfection.

The bottom line, said Gao, is that more than 50 percent of MDR and XDR TB patients represent new cases. The evidence is strong that MDR and XDR TB are being transmitted among individuals, and even some previously treated patients show primary drug resistance. The conclusion to be drawn, said Gao, is that new strategies to block the transmission of drug resistance are urgently needed.

TRANSMISSION-BASED GENETIC ANALYSIS IN SOUTH AFRICA[2]

According to WHO, South Africa, a country of around 48 million people, saw 461,000 new cases of TB in 2007—about 950 cases per 100,000 population (WHO, 2009). About three-quarters of all TB cases occurred in people who were HIV-positive, and about 112,000 people died of TB in 2007. Among those coinfected with HIV and TB, 90 percent die within months if not treated. South Africa has more HIV-positive TB cases than any other country in the world, said Gey van Pittius.

WHO has estimated that MDR TB accounts for 1.8 percent of all new TB cases, although estimates presented at the workshop were closer to 5 percent. Gey van Pittius reported that 68 percent of the budget for the South Africa National Tuberculosis Program is devoted to MDR TB, as opposed to only about 4 percent for first-line treatment.

The first documented case of XDR TB in South Africa was detected in 1997. In 2008 a study of about 700 MDR TB cases showed that 14 percent were pre-XDR—that is, MDR with one of the markers for XDR—and 6 percent were already XDR (Mlambo et al., 2008). It took 13 years from the introduction of rifampicin for TB treatment in 1972 for the first MDR TB case to arise in 1985 in South Africa, said Gey van Pittius, and another 12

[2]This section is based on the presentation of Nico C. Gey van Pittius, Stellenbosch University.

years for the first XDR TB case to appear in 1997. Now TDR TB is starting to appear after another 12 to 13 years.

Cape Town, where the Centre of Excellence for Biomedical Tuberculosis Research is located, has one of the highest incidences of TB in the world. The Centre has been working in many areas of TB research, including pharmacology, genetics, bacteriology, immunology, and molecular epidemiology. At the Centre, the mycobacterial molecular epidemiology and genomics group has been looking at the evolution of mycobacteria, pathogenicity, genomic variation, non-tuberculous mycobacteria, mycobacterial diagnostics, and drug resistance. Over the years, the group has acquired a large mycobacterial sample bank from study sites throughout Southern Africa.

In the Cape Town suburbs of Ravensmead and Uitsig, Gey van Pittius and his colleagues have collected more than 8,500 isolates and have used restriction fragment length polymorphisms to identify more than 875 different strains of *M.tb*. These strains can be grouped into 40 different strain families, which in turn fit into the strain families found throughout the world. However, two families make up the majority of their strains: the F11 strains within the LAM group and the typical Beijing strains within the Beijing group.

The strain populations within this community have changed over time. Many have declined in numbers, while some have increased. Most alarming, the Beijing strains have increased with a doubling time of 3.9 years (van der Spuy et al., 2009). This doubling phenomenon is not due to drug resistance, as only drug-sensitive strains were included in this study. In particular, a recently evolved sublineage of the Beijing strain family is associated with the increased ability to spread and cause disease within this community (Hanekom et al., 2007).

Different MDR TB sublineages are associated with specific host populations in South Africa. In the Eastern Cape Province, for example, the majority sublineage is atypical Beijing, whereas in KwaZulu-Natal, the predominant MDR TB strain is F15. In Johannesburg, the strains are more mixed. In the Western Cape Province, four major strains are responsible for much of the MDR TB—the typical Beijing strain R220, the LAM strain F11, the S-family strain F28, and the low-copy clade strain DRF150 (Streicher et al., 2004). For all of the drug-resistant TB in the Western Cape, the doubling time is 8.19 years, whereas for MDR TB, the doubling time is about 4 years. More alarming, a single Beijing strain, the R220 sublineage, is responsible for 42 percent of the total drug resistance epidemic and has a doubling time of only 2.38 years. Furthermore, 90 percent of patients infected with MDR TB strains are smear positive, which indicates that they have the potential to spread these resistant strains rapidly.

Even where the TB control program is strong and patients are adherent to therapy, XDR TB has a tendency to emerge. In a study of a mining

community in northwestern South Africa, for example, with a more than 85 percent cure rate and semiactive case finding, TB patients were put on first-line treatment before it had been determined whether they had MDR TB (Calver et al., 2010). Pyrazinamide resistance was acquired very rapidly. Since these patients in effect received only ethambutol monotherapy (because of the resistance of the bacterium to the other three constituents of the first-line therapy—isoniazid, rifampicin, and pyrazinamide), ethambutol resistance also evolved rapidly. Once the patients had been identified as having MDR TB, they were given second-line treatment. Only ofloxacin, kanamycin, and ethionamide were active (resistance to pyrazinamide and ethambutol already having developed). Then second-line resistance emerged, followed by XDR TB. This progression was especially alarming, said Gey van Pittius, because there was effective control over the patients, and adherence to therapy was very good. The overall transmission rate in this setting was 71 percent.

MDR TB is evolving into XDR TB in common strains in a number of places in South Africa. MDR TB in these settings is largely transmitted, whereas there is currently less transmission of XDR TB and more development of XDR TB from the large pool of MDR TB cases.

Specific mutations can provide insight into treatments for MDR and XDR TB. For example, a mutation in the *inhA* gene or promoter region generally confers low-level isoniazid resistance, creating the possibility of treating patients with high doses of isoniazid. This mutation is widespread in the Western Cape Province. However, this mutation also provides high-level ethionamide resistance, so that ethionamide treatment should be discontinued in these individuals. Similarly, a mutation in the *KatG* gene indicates treatment not with isoniazid but with ethionamide if the strain is found to be susceptible to ethionamide by drug susceptibility testing, as mutations in *KatG* do not confer resistance to ethionamide.

The conventional wisdom is that resistance to ethambutol is rare, so second-line treatment includes ethambutol, pyrazinamide, ofloxacin, amikacin, and ethionamide. However, a 2006 study showed that 20 percent of drug-resistant MDR TB isolates were already resistant to ethambutol (Johnson et al., 2006). Likewise, Gey van Pittius cited unpublished results from a 2008 review of MDR TB isolates indicating that approximately 50 percent had mutations in the *embB* gene conferring resistance to ethambutol.

Although the extent of pyrazinamide resistance is currently unknown, a 2006 study found that 53.5 percent of drug-resistant isolates were already pyrazinamide-resistant (Louw et al., 2006). An association also was found between pyrazinamide resistance and MDR TB. A later study found that 52 percent of MDR TB isolates showed resistance to the drug (Mphahlele et al., 2008). For these reasons, Gey van Pittius and colleagues recommended

that ethambutol and pyrazinamide not be regarded as effective second-line drugs and that drug susceptibility testing be implemented for all TB cases to ensure appropriate treatment and thereby limit amplification of resistance (Hoek et al., 2009).

Gey van Pittius noted that during the time it took to deliver his talk, four people in South Africa had died of TB—one person every four and a half minutes on average. "We are losing the battle against resistant TB," he suggested. And although transmission of XDR TB is relatively uncommon at present, Gey van Pittius believes that, given the rapid spread of MDR TB, XDR TB is likely to take hold among susceptible populations. Molecular methods will be needed to determine what types of treatment will be effective.

In response to a question about multiple infections in a single patient, Gey van Pittius said infection pressures are so high in some communities that patients are frequently infected with multiple TB strains. Sometimes the strains compete, but sometimes infection with a new strain makes a previous strain more active. A workshop participant pointed out that different strains can be found in different parts of the body—for example, in sputum and in TB lesions. In addition, Gey van Pittius noted the association between particular strains and population groups. The relationship is complicated by the varying virulence of different strains. According to Gey van Pittius, interplay between the host genetics and the bacteria is involved. Further, *M.tb.* is not known to recombine, a fact that Gey van Pittius termed "one of the lucky things in the mycobacterial research field."

A workshop participant pointed out that children often acquire TB strains different from those of their presumed adult contacts. As a result, a child may have drug-susceptible TB when a parent has drug-resistant TB, meaning that the child can be treated with less toxic and more effective first-line drugs rather than more toxic and expensive second-line drugs.

REDUCING NOSOCOMIAL DRUG-RESISTANT TB TRANSMISSION[3]

Every case of MDR and XDR TB that is prevented represents one less patient who will require 18–24 months of difficult and expensive treatment, said Nardell. Effective prevention requires consideration of the priorities in infection control. For example, if reinfection is driving the epidemic, how effective can isoniazid be for prevention? If reinfection is as common as appears to be the case, what is the potential for a new vaccine? Is there a vaccine that is better than natural infection? And how can community-

[3]This section is based on the presentation of Edward A. Nardell, Harvard Medical School and Brigham and Women's Hospital.

based care get people out of hospitals where they are transmitting drug-resistant strains among each other?

Even in places such as Peru that have good DOTS programs and effective nationwide MDR TB treatment, the number of MDR TB cases continued to rise until recently. There are probably several reasons for this, said Nardell. Standardized treatment may have contributed to the increase in drug resistance. Echoing Gao, however, Nardell noted that another major factor is that many previously treated individuals are being reinfected, even though their cases are being misclassified as acquired (i.e., secondary to poor case management). Thus while the global TB community has emphasized the need for excellent treatment adherence, transmission is in fact very important to stemming the tide of drug-resistant TB.

In places such as Tomsk, data showing a downward trend in MDR TB are encouraging, said Nardell. Yet he also cited a study based on the hypothesis that an association between substance abuse and nonadherence increased MDR TB in Tomsk; however, the major driving factor behind MDR TB appeared instead to be hospitalization (Gelmanova et al., 2007). Indeed, adherent patients hospitalized in the course of treatment were six times more likely to develop MDR TB. Nardell said this finding should be a strong message that the hospital is not a place to treat MDR TB in the long run. (See Box 4-1 for a case example of control of nosocomial transmission of TB in the Russian Federation.)

Nardell noted that the most well-known outbreak of XDR TB took place in KwaZulu-Natal Province in South Africa, where many patients at the Church of Scotland Hospital and other hospitals in the region were infected. Mortality was very high and very rapid. The majority of these patients had undergone no previous TB treatment, all were infected with HIV, and most had the same KwaZulu-Natal strain.

Health care workers also are at risk of infection. A 9-year study in Samara Oblast showed a TB risk of 742 per 100,000, 10 times that of the general population (Dimitrova et al., 2005). In inpatient TB facilities, the incidence ratio was almost 18 times that for general health care workers. This additional risk to health care workers has serious implications in places like Africa where it is very difficult to get people to work in TB hospitals. Transmission among health care workers also is a way of monitoring the spread of TB. "It is clear from this kind of data that hospitals provide a unique focus for transmission," suggested Nardell.

As early as 1986, Nardell published a study of TB reinfection among non-HIV-infected people in a homeless shelter (Nardell et al., 1986). Although such studies are difficult, they have important implications. If reinfection is occurring in institutions, people need to be treated in their homes and communities. Such treatment is occurring in a growing num-

BOX 4-1
Control of Nosocomial TB Infection in a TB Dispensary in Vladimir Oblast, Russian Federation[a]

Elina Sevastyanova, Central TB Research Institute (CTRI) of the Russian Academy of Medical Sciences, presented on control of nosocomial TB infection in the TB Dispensary in Vladimir Oblast, about 200 kilometers east of Moscow, as an example of good practices.

According to measures of occupational risk, said Sevastyanova, laboratories are the most dangerous places in hospitals in which to contract TB, followed by emergency rooms, inpatient facilities, general medical wards, and outpatient facilities. Because of these risks, hospitals need to take steps to prevent the transmission of infectious diseases within the institution, such as surface disinfection, waste disposal, and use of disposable tools. Yet these measures cannot eliminate the transmission of *M.tb.* through the air. To prevent the transmission of TB, then, health care institutions need to take systemic and long-term measures based on prioritization of resources and analyses of transmission risks.

Before 2002, the wards at the TB Dispensary in Vladimir Oblast had beds with no separation, neither active ventilation nor respirators were in use, and personnel had limited awareness of appropriate infection control measures. That year an infection control program was launched, consisting of several linked components. Zones with a high risk of contagion were designated, staff were given respirators to wear, and visitors were given masks. The premises were equipped with shielded bactericidal lamps that could be switched on when staff and patients were present, and the ventilation system was reconstructed. Patients were divided according to their level of epidemiological risk, with the most contagious being isolated. Staff implemented protocols for the timely detection, isolation, investigation, and treatment of people potentially infected with TB. For example, signs would alert staff and visitors to high-risk areas so they would wear respirators or masks. All staff and patients received regular training on preventing contamination.

At the beginning of the program, the incidence of TB cases among

ber of places around the world, reducing opportunities for institutional transmission.

Prompt and effective treatment stops transmission, Nardell pointed out. In a series of experiments conducted since the 1950s, researchers have exposed guinea pigs, which are highly susceptible to TB, to the air from patients in TB wards. In all of these experiments, just a few patients accounted for most of the infections in the guinea pigs, while the other

medical staff at the dispensary was quite high, according to Sevastyanova, with four newly detected cases occurring in 2003. This number dropped in the following years, and in 2008 and 2009, no new cases of TB occurred among the dispensary's medical staff.

The gold standard among technical measures to control TB is mechanical ventilation to create suction zones and provide controlled air flows. These systems require a considerable investment and expert design, installation, testing, and maintenance, and many TB institutes in Russia lack the proper technologies or designs for such systems. According to Sevastyanova, however, a combination of zoning according to risk and new ventilation systems greatly reduced the risk of transmission in the Vladimir Oblast TB Dispensary.

The proper organization and collection of sputum samples is also critical. In resource-limited settings, one approach is the use of ultraviolet (UV) shielded lamps. In the Vladimir Oblast TB Dispensary, one lamp operates continuously, while the other operates only when people are not present. The lamps are maintained regularly, and the level of UV radiation is measured twice a year to ensure safe and efficient operation.

The use of personal respirators must be based on a clear zoning strategy and must be underpinned by administrative measures, said Sevastyanova. Their use is recommended only in high-risk areas and during procedures that pose a danger of contagion. Respirators can be cost-effective and efficient only if staff and patients are given the right training in their use, if annual checks are carried out to ensure that they fit properly, and if they are procured and distributed in a logical manner.

Finally, in the area of training, CTRI provides lectures, exercises focused on safety provisions, and fit tests for respirators at the Vladimir Oblast TB Dispensary. Incorporation of this material into infection control manuals could help reduce nosocomial transmission of TB, Sevastyanova said.

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[a]Dr. Sevastyanova's presentation was coauthored by Dr. Grigory Volchenkov, head physician of the Regional Anti-Tuberculosis Dispensary, Vladimir Oblast.

patients were much less infectious. In almost all cases, the infectious patients were the ones with unrecognized or inadequately treated drug-resistant TB. For example, in a recent set of experiments in South Africa, 360 guinea pigs were exposed to 26 patients who were strongly smear positive, had cavitary TB, and had recently started on therapy. Among the infected guinea pigs from which spoligotypes could be obtained, all were infected by three patients later found to have had XDR TB and not to be on effective treat-

ment. "Treatment has a very profound and very rapid effect," said Nardell. "We act in hospitals now as if all smear-positive patients are infectious. In fact, if they are on effective treatment, they are not."

Conventional thinking about TB in low-prevalence areas is that people are infected and have dormant TB that is later reactivated. But in high-prevalence parts of the world, people may have a certain amount of immunity to TB by virtue of prior exposure, or some of the strains may be somewhat attenuated because of drug resistance. In such cases, reinfection may be driving the epidemic more than the original infection. According to Nardell, "You get a critical infection in some part of the lung or with some strain that allows infection to progress. That's a very different pathogenesis, where reinfection is absolutely part and parcel and not an unusual phenomenon at all."

If patients with unsuspected or inadequately treated drug resistance cause most transmission, general medical practices need to be rethought, said Nardell. Many hospitals throughout the world have open wards, which can allow unsuspected and untreated TB to spread widely. In one study done in Peru, 250 patients admitted to a female ward over the course of a year were screened for TB regardless of why they had entered the hospital (Willingham et al., 2001). Among that group, 40 patients had positive cultures; 26 of those 40 patients were smear positive; 13 of the 40 were unsuspected cases of TB; and 8 of the 40 had MDR TB, including 6 whose MDR TB was unsuspected.

Even in TB hospitals, undiagnosed drug-resistant TB is transmitted during the months it takes to receive the results of drug susceptibility testing. And in MDR TB wards, the patients who will be spreading TB are the undiagnosed, unsuspected, untreated XDR TB patients.

These observations have major implications for rapid diagnostics, said Nardell. "If we can have a tool that will quickly diagnose, we can triage, we can treat, and we can probably do a much better job than our traditional approaches with ventilation and isolation rooms," he said. Simple approaches can work. In the triage scheme that Farmer and his colleagues in Haiti have used for more than a decade, most patients are treated in the community and not in the hospital. Those who are in the hospital and are diagnosed are placed on treatment, after which they quickly become noninfectious. If they are smear negative, they can be put in the general medical ward, even if it contains HIV-positive patients, because they are smear negative and on treatment. If they are smear positive and HIV-negative, they go to a special TB pavilion with better ventilation, UV air disinfection, and so on. If they are both smear positive and HIV-positive, they go to one of six isolation rooms.

Nardell acknowledged that this is not the optimal triage scheme for every setting. In the case of MDR TB, for example, the situation is more

complex. However, having a rapid diagnostic—beyond a sputum smear and an HIV-positive test—would make it possible to develop a rational scheme for separation and treatment that could limit transmission in hospitals much more effectively than negative pressure ventilation and isolation rooms. Tests such as Gene Xpert TB and the line probe assay are rapidly becoming available in resource-limited settings. The frequency of nosocomial transmission also calls for changes in the design of hospitals and clinics, said Nardell. In climates where doors and corridors can open to the outside, constructing hospitals with many small rooms connected to each other increases the possibility of transmission. Simple negative pressure ventilation systems and the use of respirators can be implemented in all countries at reasonable cost. Germicidal UV light presents more complex issues. It is important in cold climates where ventilation is expensive, but must be used properly. Better UV fixture designs are needed, as are locally produced UV fixtures. Although the practice is common in Eastern Europe, Nardell observed that there is no need to irradiate a room once a patient leaves because people cannot be infected from surfaces. Once organisms land on a surface, it is almost impossible to resuspend them in a particle size that can be inhaled into the alveoli. Also, devices that filter air should be avoided because they generally are not moving enough air to be highly effective and provide a false sense of security.

Nardell cited a summer course at the Harvard School of Public Health for engineers, architects, administrators, and physicians on the design of safe buildings for infection control (see https://ccpe.sph.harvard.edu/request.cfm). He also highlighted the website Global Health Delivery Online (http://www.ghdonline.org), a free online resource on MDR TB and TB transmission control. This website contains discussions on topics monitored by international experts and free guidelines and documents.

During the discussion period, Nardell and Cassell discussed efforts by the U.S. Department of Defense to develop air samplers for infectious agents. Nardell noted that the main difficulty with such samplers is distinguishing living from dead organisms in the air. Infectious agents typically are highly diluted in the air, which is why guinea pigs must be exposed to TB patients for weeks or months to become infected.

5

Diagnosis of Drug-Resistant TB

Key Messages

- Rapid diagnostic methods would permit more immediate initiation of effective treatment, thus reducing the amount of time that MDR TB patients are infective.
- Molecular-genetic methods, including gel-based biological microchips, can reduce diagnostic intervals to as little as 1–2 days.
- Laboratory information management systems allow use of diagnostic results to maximum advantage and monitoring of treatment results.
- The effectiveness of these laboratory information management systems would be enhanced if information could be shared in common public health databases even if the information management systems were based in different technology and software platforms.

Presentations on the diagnosis of drug-resistant TB addressed rapid diagnostic methods, the use of biochip technology, and the need for improved laboratory capacity.

RAPID DIAGNOSTIC METHODS[1]

CTRI of the Russian Academy of Medical Sciences uses both conventional and newer, rapid methods of mycobacteria identification (see Box 5-1 for an overview of current TB diagnostic methods). The conventional methods used are fluorescent microscopy and culture, which can require up to 10 weeks for culturing and an additional 4 weeks for drug susceptibility testing. During this time, physicians and patients must wait to determine how to treat the patient's TB, and this delay provides an opportunity for the disease to spread. To shorten this time, CTRI has been using commercial products that rely on culturing and on molecular-genetic methods. These products can determine which strains are resistant or sensitive to specific drugs through colorimetric methods, with automatic detection and no use of test tubes, and reduce the time required to obtain drug susceptibility results to 6–13 days.

The molecular-genetic methods rely on detection of mutations in the DNA of *M.tb*. that convey drug resistance. One such method uses biochips developed in Russia (see the next section). It involves the extraction of *M.tb*. DNA, two-stage polymerase chain reaction (PCR), hybridization with amplicons labeled with fluorescent marks on the biochip, and detection of results using an analyzer with subsequent computer processing.

A comparison of biochip and culture data showed a concordance of 95 percent for rifampicin resistance, 88.5 percent for isoniazid resistance, and 87 percent for fluoroquinolone resistance. These are reassuring numbers, said Larionova, since not all mutations responsible for resistance are found using biochips.

Other molecular-genetic methods used to detect drug resistance involve DNA-strip or related technologies. They rely on DNA extraction, amplification by PCR, hybridization on strips, and visualization and estimation of results. These methods are highly safe, easy to use, and cost-effective. Results are available within 1–2 days and can be obtained from either solid or liquid media. A comparison of results from biochips and DNA strips demonstrated full concordance.

The above technologies allow for the detection of MDR and XDR TB during a patient's examination and the administration of adequate chemotherapy regimens to shorten the sputum conversion period, improve treatment outcomes, and prevent the spread of disease. Experience at CTRI indicates that 64 percent of new MDR TB cases convert after 2 months of treatment and 87 percent after 6 months of treatment.

New methods are also being used to diagnose infection with nontuber-

[1]This section is based on the presentation of Elena Larionova, Central TB Research Institute, Russian Academy of Medical Sciences.

BOX 5-1
Some Diagnostic Methods Currently in Use for TB[a]

Microscopy smear. Experience has shown that microscopy can detect TB, but the sensitivity is variable and can be very low.

Culture/phage based. Culturing bacteria takes longer than a smear test but is more sensitive. Smear-negative but culture-positive tests allow for earlier treatment and a reduction in transmission.

Molecular, bacteria based (e.g., PCR). Many reports on the performance of PCR in diagnosing TB have appeared since 1985. Positive results from these types of tests do not guarantee live bacteria, and repeatability issues have arisen. Specificity and sensitivity depend on the kind of sample, the kind of test, and the manufacturer. PCR may not be much better than culture for "difficult samples" such as pleural fluid or urine, and the sample preparation method can generate problems. According to Paul van Helden, Stellenbosch University, PCR also can be very expensive unless a cartridge-based test is used, and even the cost of a cartridge-based PCR test, at about US$40 or more per person, is unaffordable in the developing world. PCR has a number of applications beyond the diagnosis of TB. Scientists and clinicians can use it as a basic research tool, to assign isolates of *M.tb.* to a particular strain, and to obtain drug resistance information. Furthermore, many applications can be automated to reduce costs. In the future, for example, multiple fluorescent probes might generate considerable information simultaneously, said van Helden.

DNA based. As mentioned in Chapter 2 (Box 2-1), since the workshop was held in Moscow, a new, fully automated DNA test (Xpert MTB/RIF) for TB has been validated and subsequently recommended by the WHO for broad implementation as the initial diagnostic for individuals suspected of having MDR TB or HIV–TB coinfection. The test simultaneously detects TB and rifampicin drug resistance (a reliable indicator for MDR TB) in sputum. WHO reports that FIND has negotiated a reduced price for 116 low- and middle-income countries (including South Africa, Russia, India, and China) of US$16.86 per test cartridge. The test provides results in 100 minutes, allowing proper treatment to begin immediately (WHO, 2010d).

SOURCE: IOM, 2011.

[a]The information provided in this box was originally presented by Paul van Helden, Stellenbosch University, and summarized in the IOM Drug Forum's second workshop on the subject of drug-resistant TB held in 2010 in Pretoria, South Africa (IOM, 2011).

BOX 5-2
New Methods for Species Identification of Nontuberculosis Mycobacteria[a]

Infection by nontuberculosis mycobacteria is the cause of mycobacteriosis, a frequent opportunistic infection in patients with AIDS. New liquid culture-based automatic systems and molecular-genetic systems have made it possible to identify both NTM infection and the species of NTM involved.

The gold standard for NTM detection today is sequencing of the bacterial genome, but not all laboratories are equipped with DNA sequencers. Restriction fragment length polymorphism analysis using PCR is much more commonly employed, and several commercially available test systems exist.

Mass spectrometry is another technology used to identify NTM species. Smirnova is involved in an effort to identify NTM strains by direct protein profiling using mass spectra for ribosomal proteins. She and her colleagues have collected 35 strains of NTM and have characterized each using several methods, including microbiological, PCR-based, and mass spectrographic techniques. Accumulation of mass spectrometry data for conserved proteins will allow for the creation of a database that can be used for species identification.

Little information about mycobacteriosis is available in Russia, said Smirnova, and species identification of mycobacterial cultures is rarely performed in bacteriological laboratories. In addition, no molecular-genetic systems are available for the quick and inexpensive identification of NTM. Spectrographic determination may offer a way to fill this gap.

culosis mycobacteria (NTM) and to identify the species of NTM involved. Box 5-2 summarizes a presentation on this subject.

In the discussion period, Maria Y. Giovanni of the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health (NIH), noted that NIAID supports a comprehensive program of research and development in diagnostics. She also suggested that all diagnostics still need to be faster, easier to use, and less expensive. Kathleen Eisenach, University of Arkansas, pointed out that the Institute of Tropical Medicine in Antwerp does quality control testing for drug susceptibility tests worldwide. A panel of isolates, including MDR TB strains, is circulated to laboratories once or twice a year, which provides an opportunity for proficiency testing. “These coordinated efforts help us have confidence

Many other questions surround the diagnosis and treatment of NTM infection. How can drug susceptibility testing for NTM be performed? Who should treat patients with mycobacteriosis, where should they be treated, and how, given that mycobacteriosis is not TB? Physicians are insufficiently educated in the diagnosis and treatment of patients with mycobacteriosis, and delays in diagnosis and treatment can lead to severe and progressing disease.

In the discussion period, Carlos Pérez-Vélez of the National Jewish Hospital, Denver, Colorado, commented on the treatment of mycobacteriosis at the hospital, which typically has 10 such patients who have been referred from around the world. An interdisciplinary team of pulmonologists and infectious disease specialists manages these patients, who usually require prolonged courses of multiple antibiotics. Success for these patients depends on susceptibility testing, the management of adverse effects from antibiotics, and pharmacokinetic studies of individual patients. "The same doses in people of similar weight [and other characteristics] can vary, so sub-therapeutic dosing is really a problem in nontuberculous mycobacterial infections," said Pérez-Vélez. Many patients with MDR TB actually have an NTM infection that is resistant to isoniazid and rifampin, and some people have a mixed infection, he noted. These mixed infections can be very difficult to diagnose, since one bacterium can outgrow and overshadow another.

[a]The information presented in this box is based on the presentation of Tatiana Smirnova, Central TB Research Institute, Russian Academy of Medical Sciences.

in the drug susceptibility testing that is being performed at all levels in all countries," she said.

Several participants discussed the prospects for diagnostics that use sputum or some other sample and do not involve culturing. Coetzee noted that several technologies do not require culturing and have produced good results. However, they do not work as well in HIV-infected patients, who have a lower smear-positive rate than other TB patients.

Several participants compared the cost of diagnostics with the cost of treatment. Given the expense of second-line drugs, even quite expensive diagnostics may be cost-effective. "A day of capreomycin, even at discount rates, costs $3 to $5," said Cassell. Therefore, she suggested, it makes no sense to wait for a $1 test. Accurate diagnostics also could obviate the need for expensive follow-up tests.

Keshavjee pointed out that airline security systems now rely on mass spectrometers to detect bomb-making chemicals within a few seconds. In an ideal world, a TB diagnostic would produce results instantly so that the proper treatment could be initiated at the point of care. Even if diagnostic technologies are not perfect, they can suggest a treatment at the point of care, and that treatment can be modified once more definitive results are available.

BIOCHIP TECHNOLOGY FOR TB DIAGNOSIS[2]

Gel-based biological microchips were developed by Andrei Mirzabekov at the Engelhardt Institute of Molecular Biology in the early 1980s, and much progress has been made on their further development since then, said Zimenkov. Today, biochips are based on three-dimensional gel pads on a plastic surface rather than two-dimensional glass surfaces, which increases the sensitivity of analysis and leads to excellent discrimination levels. Point mutations are detected by DNA hybridization on the biochip, with fluorescence intensities being compared to determine whether tested DNA bears a particular mutation. Software is user-friendly for medical personnel, and the biochip analyzer has been certified in clinical trials.

In 2001 the Institute of Molecular Biology received support from the International Science and Technology Center (ISTC) to study the application of biochips in TB diagnostics for fast discrimination and strain typing of MDR TB in Russia. Biochips were developed to detect mutations leading to resistance to rifampicin and isoniazid. The chips were able to identify more than 95 percent of rifampicin-resistant TB strains and more than 80 percent of isoniazid-resistant strains. Since being certified in 2004, the biochip has been used in more than 10,000 analyses.

The use of biochips has had a major impact on treatment. When biochips were used to determine second-line treatments in MDR TB cases, healing, or bacterial conversion, was approximately twice as rapid as when classical methods were used, according to Zimenkov (Kuzmin et al., 2006). Similar results were obtained in a comparison of three groups: one consisting of people resistant to one or two drugs who received the standard treatment, one consisting of MDR TB patients who received the standard treatment, and a third treated after biochip analysis (Morozova, 2008).

A more recently developed biochip detects mutations involved in resistance to fluoroquinolones in about 80 percent of strains. Thus far it has been used in more than 3,000 analyses in Russia and other countries. New

[2]This section is based on the presentation of Danila Zimenkov, Engelhardt Institute of Molecular Biology.

chips being developed detect additional mutations involved in fluoroquinolone resistance.

Biochips also are being used to perform automated analyses of repeated units in the DNA of *M.tb.*, allowing different strains to be distinguished. For example, the technology can distinguish *bovis* strains from Beijing strains in about a day. The technology can now distinguish among more than 100 strains of the bacterium, making it possible to determine the extent to which strains are mixed in patients. This technology is being extended to produce a biochip for mycobacteria differentiation.

In the discussion period, several workshop participants expressed interest in the biochip, which was developed in part through a partnership with Argonne Laboratory in the United States. Jeffrey Drazen, *New England Journal of Medicine*, urged that quantitative research techniques be used to study the biochip to determine its sensitivity and specificity relative to standard diagnostic techniques. Drazen said that this type of information would move the field from descriptive to quantitative research and would be a positive step forward in terms of the scientific development of diagnostic techniques.

NEED FOR IMPROVED LABORATORY CAPACITY[3]

WHO's Global Laboratory Initiative (GLI) has identified the need for an urgent and massive scale-up of TB laboratory services. According to the GLI, "The global lack of TB laboratory capacity constitutes a global crisis, requiring a paradigm shift in providing laboratory policy guidance, quality assurance and knowledge creation within a global and integrated laboratory network." Some of the challenges and successes of improving laboratory diagnostic capacity are illustrated in Box 5-3.

Several critical issues surround global laboratory capacity, Nordenberg said:

- Laboratory capacity is desperately insufficient.
- Laboratory capacity-building efforts rarely consider data and information management.
- Laboratory programs are focused on specimens and therefore have information system requirements very different from those of clinical or public health programs.
- Emerging diagnostics can change surveillance methods or the sensitivity and specificity of both TB and drug-resistant TB testing,

[3]This section is based on the presentation of Dale Nordenberg, Novasano Health and Science.

which in turn affects surveillance trend estimates and outbreak control.

- There is a critical need to integrate the information systems of laboratories, clinics, and public health programs.
- There is a critical need as well for "operations" systems to track such activities as infection control programs and therapeutic supply chains.

BOX 5-3
Diagnostics and Laboratory Infrastructure in South Africa[a]

Dr. Coetzee discussed South Africa's latest efforts to organize laboratory services for the effective diagnosis of drug-resistant TB. In South Africa, simultaneous infection with HIV and TB has created a widening gap between smear positivity and TB cases. As a result, smear microscopy is rapidly failing as a diagnostic tool and will soon become unusable, Coetzee said, emphasizing that new diagnostics are desperately needed to combat drug-resistant TB. In 2006 WHO held a meeting in South Africa that generated a recommendation to develop and implement rapid diagnostics throughout the country. In response, South Africa invested heavily in line probe assays (LPAs).[b] Currently, line probes are running in 15 laboratories, and they will be available in 10 more before the end of 2010. However, this scaling up of LPA capacity is an extremely difficult task. A significant challenge is the country's workforce constraints, in particular the small number of molecular biologists. The probes also were placed in laboratories with good ventilation and working environments, and such facilities are among the top few percent of African laboratories, said Coetzee.

The performance of the implemented line probes has been high. However, the reading of the line probes had to be standardized. "We found inter-observer errors in PhDs, so you can imagine what the rate would have been in technicians," said Coetzee. The line probes are scanned and interfaced with the laboratory information system, which has produced standardized results.

The National Health Laboratory Service has about 350 laboratories, and all of the public-sector laboratories have been consolidated into one organization. This consolidation has enormous benefits for surveillance. The development of an algorithm for the early detection of MDR TB was a politically challenging process, Coetzee said. In the end, however, a policy was established that a line probe will be administered to every new smear-positive patient. If a patient is smear negative and culture positive,

The challenge, said Nordenberg, is that these issues apply not just to one or two but to thousands of laboratories. To stop the spread of TB globally, the world needs rapid, accurate diagnostics, particularly in resource-poor settings. Also needed are drugs that will shorten treatment, be effective against both susceptible and resistant strains, be compatible with antiretroviral therapies, and improve the treatment of latent infection; a vaccine that is safe and effective for children, adolescents, and adults,

the culture will undergo a line probe. This is an expensive process, but less so than first-line drug susceptibility testing.

The infrastructure in much of South Africa is rural, with scattered electricity and water supplies. However, cell phone reception is often available. The country has begun using cell phone printers, through which messages can be exchanged. With the rollout of the line probes, TB facilities throughout the country began using a new form that makes it possible to follow patients longitudinally through the system and monitor their adherence to the TB control program. Information from the forms is migrated to a central data warehouse in Johannesburg to produce a single consistent view of the data. Information includes all demographic data, all test results, all drug susceptibility test results, and billing information. The new system is still being piloted, but Coetzee said the hope is that it will improve adherence to policy.

Making the transition from specimen-based to patient-based data has been difficult. Demographic information is often inadequate or inaccurate. Data security and the user interface required considerable work. Some of the data contained in approximately 12 million records had to be checked visually.

The system also is being used for other infectious diseases in South Africa, such as cholera and meningitis. Notification of an outbreak is automatic through web-based portals. Reports can be generated by province, by district, by subdistrict, or by clinic. South Africa is now enhancing its reporting for national health programs focused on HIV, TB, cervical cancer, and sexually transmitted diseases. It also is working to improve the spatial reporting of infectious diseases to assist various health authorities.

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[a]The information in this box is based on the presentation of Dr. Coetzee.

[b]Line probe assay technology involves the isolation of DNA from sputum specimens for the rapid detection of MDR TB.

including people with HIV; and efficient and sustainable information supply chains (discussed below).

The New Diagnostics Working Group of the STOP TB Partnership has identified several critical attributes of TB diagnostics (WHO, 2009), finding that such diagnostics should:

- simplify and improve the detection of TB, including smear-negative, extrapulmonary, and childhood TB, through increased sensitivity and specificity and improved accessibility;
- offer simple, accurate, safe, and inexpensive tests that can be performed at the point-of-care level of the health care system and produce same-day results;
- enable more effective monitoring of TB treatment for both latent and active cases;
- rapidly identify resistance to both first- and second-line TB drugs; and
- reliably identify latent TB infection and determine the risk of progression to active disease, enabling the rational use of preventive therapy.

Nordenberg suggested that information should itself be seen as an intervention. The supply chain needs to get the right therapeutics to the right patient. If a diagnosis is not used to drive treatment, a major opportunity is being missed. If cases are identified earlier, less resistance will develop, patients will be less costly to treat, and fewer people will spread the infection. Thus, the return on investing in information infrastructure is very high. "Without that investment, all the investment in diagnostics is compromised," said Nordenberg.

The data produced by diagnostics can have a major impact on public health, but they need to be collected, managed, and shared. Doing so means moving across what Nordenberg called the "information chasm" from laboratories to epidemiological and public health impact. Crossing that chasm requires laboratory information management systems. Such a system is a tool that supports the work of laboratories as opposed to that of clinicians or health epidemiologists. A laboratory information management system needs to perform a diverse set of functions—test requisition, test receipt documentation, sample management, testing and validation, report distribution, report receipt documentation, test scheduling, sample collection, chain of custody, reagent management, quality assurance, and others. These functions are not in the domain of a clinician or epidemiologist. With influenza, for example, various types of tests can be performed on a given specimen. A laboratory information management system has to document and be the repository of results from this complex analytic process.

About 80 percent of the 50 public health laboratories across the United States have a laboratory information management system, after about 7 years of implementation efforts. Each state is implementing its own system, while approximately five to seven different primary systems cover the 50 states. The laboratories perceive that they have differing needs with regard to public health priorities, bench methodologies, and technologies. This is also the case internationally; some countries in Africa, for example, are implementing two or three different systems, even within the same city.

With the emergence of new technologies and new diagnostics, moreover, local laboratories are conducting more of their analyses locally and sending fewer specimens to regional or national laboratories for analysis. As a result, local laboratories are starting to build their own data-sharing networks. These networks need to be integrated with clinical, public health, and other research activities. They also need to be able to handle not just TB but also other infectious diseases. A public health laboratory is typically responsible for a broad spectrum of programs, and a laboratory information management system needs to support that mission. Nordenberg used influenza as an example. More than 60 tests are used to describe and manage an influenza epidemic. To facilitate data exchange, the national laboratory community has made more than 500 specific data-related coding decisions. Nordenberg emphasized the importance of being able to share diagnostic data, which requires such collaboration.

Even though laboratories are working with different technology platforms, they are identifying common data that they will share, so the information kernel is standard. This kernel, derived from a description harmonized by a community, must adjust dynamically as new scientific methodologies and technologies emerge. Even before the first version of a product has been fully implemented, new versions can appear that overlap with the previous versions. At any given time, multiple versions may be in use. Only through ongoing collaboration can a systems approach produce an alignment of vision, mission, and execution.

Nordenberg emphasized that a public health information supply chain is not an abstract concept, but something that must be engineered through a comprehensive, logistics-based approach. In particular, a disciplined approach to data and information provisioning will enable measurement of the quality and impact of the data, allowing performance to be improved.

A systems approach, in contrast to an ad hoc approach, can produce several additional capabilities. A systems approach is scalable, so that it can meet the need for robust information supply chains in thousands of laboratories across the globe. It is intentionally designed to be dynamic so that it can be optimized through continuous performance improvement. And it provides the ability to integrate data across laboratories, clinical programs, and public health programs. A systems approach transcends a

vertical, single-disease approach and can support diverse health care priorities and programs.

Nordenberg outlined additional important capabilities of a laboratory information management system:

- it must be sustainable;
- it must be cost-effective;
- it must leverage and build local expertise;
- it must be driven by public health and science, not just by technology;
- it must be governed by stakeholders; and
- it must provide a clear path to robust capability while accommodating a diversity of baseline capacity.

An information supply chain is distinct from the other supply chains required to manage a TB or MDR TB program, such as people, hard goods, diagnostics, therapeutics, reagents, and so forth. Nordenberg noted that information is often overlooked when laboratory capacity is being built. As a result, systems are frequently developed in an ad hoc manner, and there is a divide between the technology platform and the ability to get the data where they are needed.

The components of an information supply chain are information products, a source of raw materials, human resources, and standard operating procedures, each of which must be articulated with the others. Information products are motivated by the questions that drive decision making, and all supply chains must reflect a clear idea of the products they need to produce. The sources of raw materials are the data systems that provide the data for information products. Human resources are the staff that build and operate the systems and develop the information products. Standard operating procedures are the processes used to manage the data to produce information. "The information supply chain is a complex endeavor," said Nordenberg. "It's much easier to buy a piece of technology, or buy a system, install it, collect the data, and then hope you get out of it what you need. But usually you are going to be disappointed."

To realize the full benefits of information systems, the laboratory, clinic, and public health entities in a given area need to work together. Nordenberg illustrated this point: "If you can get a laboratory result in 2 days or in 3 weeks, but then it takes another week to get the result of that test to somebody, that's going to have serious costs in terms of delayed diagnosis and increased spread." Especially with TB, the cost of a broken information supply chain can be calculated in both human and financial terms.

Nordenberg offered several recommendations regarding information supply chains:

- Country plans for information supply chains should be developed to support TB and MDR TB control.
- Laboratories should collaborate multinationally and sustainably to develop shared best practices.
- Plans should be developed to migrate laboratories at all levels of information technology capability to the same target capability.
- A tight linkage should exist between diagnostics development and data activities.
- Technology adoption and information capability should be tracked to guide programs.
- Metrics related to time from specimen acquisition to diagnosis and treatment should be developed and tracked.
- Information plans should be assessed annually to respond to new developments in such areas as diagnostics, drugs, and intervention programs.
- HIV and TB data systems should be integrated to support the management of coinfected patients.
- Educational programs should impart a clear understanding of the specific needs of laboratories versus clinical and epidemiological activities.

During the discussion of information systems, Coetzee, Nordenberg, and Renzhong Li of China's Center for Disease Control and Prevention discussed the degree of integration between the clinical and laboratory systems in different countries. In South Africa, said Coetzee, the systems are not integrated. Even large hospitals have systems that handle only administrative and not clinical data. A new patient management system is being implemented for lower-level clinics, which will help integrate the treatment of HIV infection and TB. Also, there are limited interfaces between hospital management systems and patient management systems. Much HIV testing is no longer done at laboratories but at the point of care, which means that previously available surveillance data have been lost. In China, said Li, data from patient care are available but not from the laboratory system.

A workshop participant asked how data from private practitioners in many countries can be integrated in the same system, since the same platform probably will not be used to communicate results. Nordenberg observed that the same situation exists in the United States, where a wide diversity of independently run systems exists in both the public and private sectors. He reiterated that effort is focused on creating an information kernel that is constant so the data can be shared even though the technologies differ. He also noted that the web-based patient-level system in China is remarkably successful, reaching thousands of different entities—from the

county, to the prefecture, to the province, to the national level—across the country.

A participant pointed out that the ideal situation is to get data from laboratories to clinicians rapidly so that treatment can begin. In some countries, this information flows via cell phone, although provisions must be made to ensure privacy. Also, private practitioners and laboratories need to be integrated into public systems.

Nordenberg responded that the most efficient way to scale up communications is through web-based systems. Implementing thousands of information systems across laboratories of varying capacity is difficult. But the problem of connectivity can be and is being solved through web-based communications. In the short term, cell phone infrastructures can suffice, particularly if systems are set up using passwords to protect privacy, according to Nordenberg. It is also important, he said, for laboratories to share best practices. For example, if different diagnostics have differing sensitivity and specificity, how does that affect estimates of incidence? How can data be shared within or across countries? How are reporting forms designed?

A workshop participant asked whether the widely varying results of drug susceptibility testing in China argue for the use of individualized rather than standardized treatments for MDR TB. Nordenberg asked whether the laboratory results are fed into the patient information system. Li responded that the patient data are referred to the TB dispensary. Nordenberg also pointed out that, despite the excellent patient information system, the lack of an integrated laboratory system in China makes it difficult to look at population trends in resistance. The challenge, he said, is to run a program focused both on resistance patterns and on patients.

6

Treatment of Drug-Resistant TB

Key Messages

- Aggressive drug therapy can increase the range of options for MDR TB patients.
- HIV infection is a major driving force behind the TB epidemic in adult populations.
- Adherence is the key to treatment success for both TB and HIV.
- The combination of aggressive drug treatment and surgery, which is widely used in Russia, can improve the outcomes of patients with MDR TB.
- An important component of an effective public health treatment program is the promotion of scientific research into new technologies and methods of diagnosing and treating patients and the rapid incorporation of scientific innovations into the program.

Clinical care is an important part of any meaningful response to drug-resistant TB. Even with XDR TB, Farmer noted, there is no escaping the clinical imperative of treating patients.

Farmer stated that XDR TB is not untreatable but is very difficult to treat, and failure rates are high even with the highest standard of care, which includes aggressive regimens that often must be tailored to patients on the basis of laboratory data. Yet the laboratory data needed to tailor

treatments often are difficult to obtain in those settings where drug-resistant TB takes its greatest toll. Other data also affect treatment regimens. For example, the degree of parenchymal damage should determine the duration and form of therapy; Russian physicians have demonstrated the importance in some cases of adjuvant surgery (see Chapter 3 and the further discussion of this approach later in this chapter). XDR TB is not a new genus or species, said Farmer. The disease is ultimately TB, and the issues that have been discussed for many years with regard to MDR TB apply also to XDR TB.

High-quality clinical care must keep pace not just with genetic mutations but also with social mutations, said Farmer. Social mutations in the Soviet Union, the United States, and other countries have been partially responsible for TB outbreaks in the past, which have consumed major resources before being brought under control. Yet the system of clinical care for drug-resistant TB has seen little innovation over the last 10 years. Most new drugs are really variants of old ones; no new class of drugs has made it through clinical trials and regulatory processes during this period. A few novel agents are in the drug development pipeline, but access to them for treatment is not yet close. Thus, as many workshop participants noted, MDR TB treatment must be provided with what is available today, tailored to the drug susceptibility patterns of patients.

Speakers addressed several topics related to treatment of drug-resistant TB: the need for tailored treatment regimens based on drug susceptibility testing, treatment of drug-resistant TB in the Russian Federation, treatment of patients coinfected with TB and HIV, and innovative research in MDR TB treatment.

PETTS: MAKING THE CASE FOR DRUG RESISTANCE TESTING AND TAILORED TREATMENT REGIMENS[1]

M.tb. has developed resistance within a few years to every anti-TB drug introduced in the past, from streptomycin and isoniazid in the 1940s and 1950s, to rifampin in the 1960s and 1970s, to the quinolones in the 1990s. As a result, said Cegielski, the GLC was established with three goals: (1) increase access to effective treatment of MDR TB with quality-assured second-line drugs, (2) prevent increasing resistance to those same drugs, and (3) contribute to the evidence base for policy guidelines.

Evaluating the GLC's impact on preventing drug resistance was the stimulus for the Preserving Effective TB Treatment Study (PETTS), which has the objective of determining the frequency of and risk factors for acquired resistance to second-line drugs in a diverse group of MDR TB programs. The study is examining the characteristics of programs (includ-

[1]This section is based on the presentation of Dr. Cegielski.

ing whether they were approved by the GLC), of patients, of the bacteria, and of the treatments received by patients. It also is seeking to determine the consequences for patients of acquired resistance to second-line drugs.

PETTS is a prospective follow-up study of MDR TB patients in nine countries: Estonia, Latvia, Peru, the Philippines, Russia, South Africa, South Korea, Taiwan, and Thailand. Consecutive consenting adults with pulmonary MDR TB, confirmed locally, are being enrolled at the start of treatment with second-line drugs. In other words, all eligible patients are informed about the study and invited to participate at the same time that they are being evaluated and started on treatment. The goal is to have the patients included in the study be representative of the patient population in general. Study participants have a baseline sputum culture taken within 30 days of the start of treatment, and follow-up sputum cultures are then taken monthly for 2 years or until treatment is complete. For consistency, all cultures are shipped to the CDC for centralized analysis.

The strategy is to compare the drug susceptibility test results for the first and last positive cultures from each patient. These isolates are tested for susceptibility to 12 drugs. If the drug susceptibilities have changed, those isolates are genotyped. If the genotypes are the same, acquired resistance is assumed; if the genotypes are different, resistance is most likely related to the strain differences.

PETTS sites are in the nine countries, with the global coordinating center being located in Atlanta at CDC. Enrollment for the study ended in December 2008, with viable and uncontaminated baseline cultures having been received from 1,398 patients. The patients differed considerably by site, but overall, 19 percent were HIV-infected (with 34 percent having uncertain HIV status), 13 percent had diabetes, 53 percent were hospitalized at the start of treatment, 83 percent were smear positive, 61 percent had cavitary lung disease, and 16 percent were cases never previously treated. Most of the patients, 71 percent, had been treated before with first-line drugs; a smaller percentage, 13 percent, had been treated before with second-line drugs.

Of the total group, 1,278 patients had confirmed MDR TB, with corresponding clinical data. Confirmation of results of local drug susceptibility testing as MDR TB at CDC's laboratories was 96–100 percent for five countries and 84–90 percent for three countries.

A large number of these patients already had showed resistance to second-line drugs at the start of treatment. Resistance was 11 percent for the quinolones, 11–18 percent for the injectable agents, close to 20 percent for ethionamide, and almost 10 percent for para-aminosalycylic acid. Resistance to second-line drugs varied greatly from country to country—for example, from 4 to 31 percent for ethionamide. The overall high level and

diversity of drug resistance found at baseline suggests that standardized approaches to treating MDR TB are not advisable, said Cegielski.

Patients also were resistant to drug combinations. For example, half of the patients showed resistance to all four first-line drugs. More than 40 percent showed resistance to at least one second-line drug, with a range of 33 to 62 percent. Twenty percent showed resistance to at least one of the injectables (kanamycin, amikacin, and capreomycin), 10 percent to all three of the injectables, and 11 percent to the quinolones. Six percent of patients had XDR TB at the start of treatment. Again, the range of resistance across sites was broad, indicating that the treatment of MDR TB should be tailored to the unique epidemiology of specific populations and ideally individualized to patients' susceptibility patterns.

Because these were all MDR TB patients, isoniazid and rifampicin could not be used for treatment. More than 60 percent of the patients already showed resistance to ethambutol and streptomycin, and 10–20 percent already showed resistance to at least one of the main drugs used in treating MDR TB. Ignoring this preexisting resistance would contribute to the development of XDR and TDR TB, said Cegielski.

Almost half of the patients were susceptible to a higher concentration of isoniazid, reflecting recent results on the efficacy of high-dose isoniazid, and 30 percent showed susceptibility to rifabutin. Microbiologists argue about whether these results are an artifact of testing or have *in vivo* significance, but Cegielski believes that these strategies should be tested in controlled clinical trials. He contends that we do not need to wait for new drugs to begin developing better treatments for MDR TB; rather, we can use drugs that are already approved and on the market more effectively. Similarly, of the patients whose TB was resistant to kanamycin, many were infected with strains susceptible to amikacin and capreomycin. Cegielski emphasized that these are *in vitro* results that need to be studied in controlled clinical trials.

When the number of drugs to which patients showed resistance is subtracted from the 12 that were tested, 4 potentially effective drugs remained for 70 percent of patients, which the WHO deems the minimum adequate treatment for MDR TB. If more aggressive and novel approaches are considered, the proportion of patients with the potential to respond to four effective drugs would hypothetically increase to well over 90 percent. Partners In Health has shown in projects around the world that treating patients more aggressively with more drugs yields higher cure rates. Especially given the toxicities of second-line drugs, being able to choose from a number of drugs is important.

Cegielski briefly discussed follow-up data on 477 isolates. The isolates have not yet been genotyped, so it is not known whether resistance was acquired, but the resistance patterns are available. From 10 to 18 percent of patients showed resistance to a second-line agent on their last posi-

tive culture that was not present at the beginning of treatment. Among patients who showed no fluoroquinolone resistance at the start of treatment, 11 percent exhibited such resistance on their last culture. Among those who initially showed no resistance to the injectables, 18 percent did so at the end of treatment. Among those who initially showed no second-line drug resistance at all, 17 percent showed resistance to at least one of the second-line drugs at the end of treatment. Also, 10 percent of patients who did not have XDR TB at the start of treatment had it at the end of the study period.

TREATMENT OF DRUG-RESISTANT TB IN THE RUSSIAN FEDERATION[2]

Vasilyeva reported on the treatment of MDR and XDR TB patients at the CTRI, Russian Academy of Medical Sciences, in Moscow. Treatment efficacy in newly detected TB patients in the Russian Federation was 57.8 percent in 2008. CTRI has 80 beds in its MDR TB department and another 50 beds in its TB department. MDR and XDR TB accounted for 40.6 and 2.2 percent, respectively, of cases at CTRI in 2008. Among previously treated patients at CTRI, 61.6 percent had MDR TB and 16.5 percent XDR TB.

As noted earlier, Russian TB patients are often treated with surgery aimed at healing lung cavities. According to Vasilyeva, when surgery (i.e., collapse therapy, artificial pneumothorax and/or pneumoperitoneum) is combined with chemotherapy based on drug susceptibility testing, better results can be obtained than with chemotherapy alone. Vasilyeva reported that treatment with chemotherapy and surgery at her institution was found to be 83 percent effective (sputum conversion) after 8 months, compared with 44 percent effectiveness for chemotherapy alone.

To illustrate, Vasilyeva presented a case study of a 27-year-old male patient who had been ill for 3 years and for whom previous therapy had produced no effect. When treated surgically and with aggressive chemotherapy based on the results of drug susceptibility testing, the patient had a negative culture and began putting on weight. In a second case study, a 21-year-old woman had been ill for 3 years with no effect of treatment, and an x-ray showed that her right lung had been destroyed. After a year of being prepared for surgery, she underwent the surgery and was treated with chemotherapy for 15 more months. At her 18-month follow-up, she was stable and culture negative.

According to Vasilyeva, treatment success depended on the length

[2]This section is based on the presentation of Irina Vasilyeva, Central TB Research Institute, Russian Academy of Medical Sciences.

of time until diagnosis of drug-resistant TB, as well as the quality of the diagnostic tool. As CTRI implemented rapid biochip methods of MDR/XDR TB diagnosis within 24 hours after sputum collection, the effectiveness of MDR TB treatment increased significantly as a result of the timely administration of second-line drugs. Vasilyeva concluded that the success of MDR TB treatment depends on the point at which MDR or XDR TB is detected, adequate long-term treatment regimens, the quality of second-line drugs, the use of surgical methods, and the early management of adverse drug effects.

DRUG-RESISTANT TB AND COINFECTION WITH HIV[3]

HIV is a driving force of today's TB epidemic, said Shin. It increases the risk of contracting TB, the risk of having disease that is drug resistant, and the risk of excess morbidity and mortality. Shin suggested that HIV infection is a major factor in the failure to control TB. Another driving force of the epidemic in many locations is the underlying vulnerability of particular populations. For example, TB and HIV infection can be intertwined with physical and mental problems, including those caused by substance abuse (see Chapter 7).

Shin discussed her experiences in Peru, where a cohort of patients treated from 1996 through the end of 2005 consisted of about 100 patients infected with HIV who were receiving treatment for MDR TB. This cohort served as something of a natural experiment, said Shin, because a supply of antiretroviral drugs for this group became available only in 2004. Most of the patients had been previously treated for TB, and the majority had AIDS, with a mean CD4 cell count of 181.

A minority of the patients were cured, with death occurring in about half of the cohort. Survival was better among those who received antiretrovirals. Shin emphasized that immune reconstitution is essential if MDR TB is to be brought under control, even though adding antiretrovirals to complex anti-TB regimens is difficult. Indeed, the literature now advocates that treatment with antiretrovirals begin as quickly and aggressively as possible.

Adherence is the key to treatment success for both TB and HIV. According to Shin, adherence must be greater than 95 percent to avoid excessive virologic failure with HIV infection, although the actual percentage varies with the types of antiretrovirals used. One potential advantage of treating a coinfected population is that an aggressive approach to achieving adherence to TB therapy can help ensure that the patient also maintains adherence

[3]This section is based on the presentations of Sonya Shin, Harvard Medical School and Brigham and Women's Hospital, and Olga Frolova, Federal TB Healthcare Delivery Center for HIV-Infected Patients, Russian Federation.

to antiretroviral therapy (ART). In Peru, for instance, community-based directly observed therapy programs reduced mortality more for people on both therapies than for those on TB therapy alone. Directly observed therapy for coinfected patients also reduced hospital admissions. Patients who received this kind of community support required only five hospital days per person-year versus 15 for other patients, thus saving costs as well.

In Russia, said Frolova, the monitoring of TB and HIV infection is combined, with the resulting data being delivered to the TB specialist responsible for HIV coinfection in the area. In a general hospital, data on such cases are transferred to this specialist, as are reports on such cases from autopsies. Confidentiality is ensured by having just one person in charge of the data, and the data are encoded. Through this system, information on patients coinfected with TB and HIV is available for all of Russia.

In a review of drug susceptibility data for about 4,500 HIV-positive patients, resistance to one drug was found in 11 percent and resistance to two or more drugs in 55 percent (about half of whom also showed resistance to rifampicin and isoniazid), and 34 percent remained drug-susceptible. Among coinfected patients, three-quarters of men and just more than half women had become infected by HIV through injecting drug use. This is an important group, said Frolova, because they can leave institutions, move to metropolitan areas, and infect other people in the community.

Frolova stated that the number of new cases of TB-HIV coinfection has been increasing over the past decade, to more than 6.5 per 100,000 population in 2009 (Figure 6-1). Similarly, the number of new cases of HIV infection in the Russian Federation has been increasing in recent years following a decline early in the 2000s (Figure 6-2). The direct cause of death for more than half of HIV-infected patients is TB.

According to Frolova, most HIV-infected patients in the Russian Federation are examined for TB. In 2009, more than 15,000 people with HIV received TB treatment, including more than 7,000 who received ART. Among those receiving ART, 12 percent were simultaneously undergoing anti-TB therapy.

Frolova cited several challenges related to treatment of coinfected patients. For example, international guidelines call for ART to be given to patients with extrapulmonary TB, but there is no universal definition of extrapulmonary TB. At the same time, patients are supposed to be given numerous antiretroviral and anti-TB drugs, but Frolova expressed concern that many suffer from severe liver disorders that interfere with drug treatment. In general, she said, there is little experience in Russia to call on in the use of antiretroviral drugs in patients coinfected with TB and HIV.

To stop the spread of TB-HIV coinfection, said Frolova, the Russian Federation must:

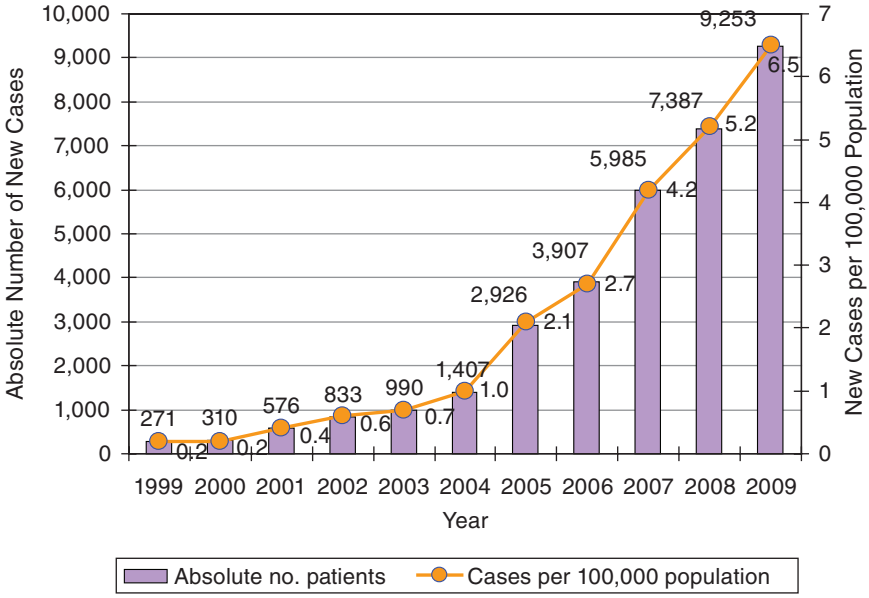

FIGURE 6-1 The number of new cases of TB-HIV coinfection in the Russian Federation has grown dramatically since 1999.
SOURCE: Frolova, 2010.

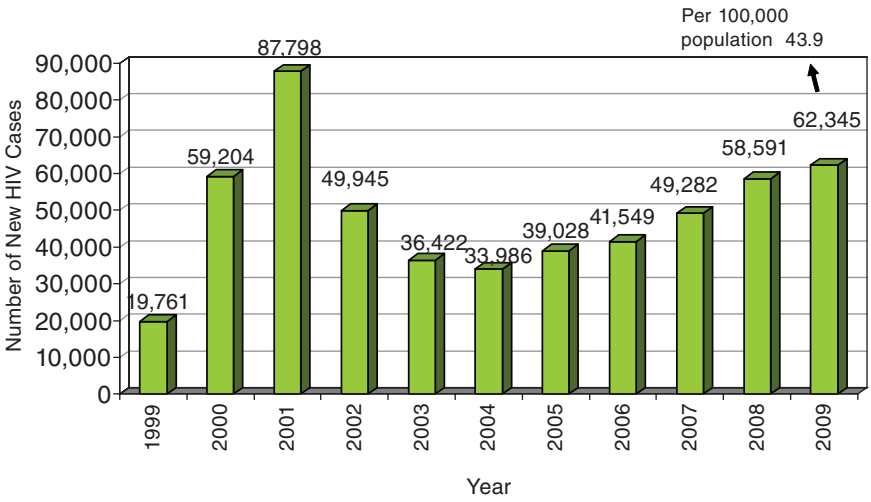

FIGURE 6-2 The number of new HIV cases in Russia declined at the beginning of the decade and began to increase in 2004.
SOURCE: Frolova, 2010.

- develop and implement a clear and strict TB control plan;
- improve legislation allowing TB control measures to be implemented;
- open inpatient facilities and hostels for patients with TB and HIV coinfection; and
- devise a system for delivering TB care to HIV patients and drug addicts along with drug services.

INNOVATIVE RESEARCH IN MDR TB TREATMENT

Speakers described two areas of innovative research in MDR TB treatment: immunological and stem cell therapy and the use of bone marrow cells.

Immunological and Stem Cell Therapy in MDR TB Patients[4]

The advent of TDR TB demands new approaches to the treatment of TB, said Maeurer. He described several recent research advances that have brought the field closer to such treatments.

In a recent experiment using nonhuman primates, three groups of monkeys received different vaccines and then were challenged with virulent *M.tb*. The first group received saline solution and acted as a control. The second received a genetically altered Bacille Calmette Guérin (BCG) vaccine, and the third received normal BCG vaccine. The latter two groups survived well compared with the control group. To identify a correlate of success, Maeurer and colleagues surveyed the immunological reactions of the monkeys. The animals that survived had a very strong gamma-interferon response. But Maeurer observed that 4,500 other antigens also could be monitored as a measure of immunological success. The questions to be answered were which antigens should be chosen, which confer protection, and whether there are any other immune correlates in the T cell compartments.

To provide at least partial answers to these questions, Maeurer and colleagues examined the cytokines released by polyfunctional T cells, which are able to make three or four different cytokines simultaneously. Monkeys with T cells capable of producing gamma-interferon, tumor necrosis factor, and antileukin-2 at the same time were well protected. Again, Maeurer asked which other proteins could provide a good measure of resistance to TB.

As part of this work, Maeurer's team used a method known as tetramer-

[4]This section is based on the presentation of Markus Maeurer, Karolinska Institute, Stockholm, Sweden.

gated detection to examine a patient infected with TB and a second patient infected with another mycobacterium. The patient infected with TB had a very specific T cell response compared with the other patient. "This opens an entirely new avenue of immune diagnostic which is fast and robust and independent of cytokines," said Maeurer.

To test a larger number of proteins, Maeurer's group extracted proteins from serum, fragmented them, and screened them using a microarray containing tens of thousands of peptides. Using just 3 microliters of serum, they were able to identify correlates of TB infection and response to treatments. For example, specific peptides were detected in 34 of 34 people with TB but not in any healthy individuals. Individuals who are infected with TB, who are not infected, and who have varying reactions to TB treatments can all be identified quickly, robustly, and with a minimum amount of serum. "This powerful technology allows us . . . to decipher who is sick, who is healthy, and what happens if we treat a patient with novel therapies or if a patient receives a tuberculosis vaccine," said Maeurer. It also is a way to identify drug treatment targets in patients who have XDR TB versus normal TB, which aids in clinical treatment and development and the measurement of success and failure.

Maeurer and his colleagues have also used IL-7 to treat patients with XDR TB. IL-7 is the most potent T cell survival factor and the most potent suppressor of TGF-beta. TGF-beta creates connective tissue, which interferes with breathing. The human immune system is "bathed" in IL-7, which is produced in the thymus, the kidney, and the intestines. When mice lack the ability to produce IL-7, they have combined severe immunodeficiency syndrome, even though the loss of other cytokines does not have such severe effects. IL-7 activates the *RAT1* and *RAT2* genes, it programs T cell development in the thymus, it helps rearrange the T cell receptor, and it is important for T cell differentiation.

More than a decade ago, Maeurer performed an experiment that involved infecting mice with *M.tb.* and then treating them with various cytokines, including IL-7. The experiment showed that mice injected with IL-7 lived much longer than those injected with other cytokines. However, the protective effect was much stronger for IL-7 cells extracted from mice already challenged with *M.tb.* than for IL-7 alone.

Injection of monkeys with IL-7 produced much higher activity in bone marrow and thymic tissue. IL-7 appears to broaden the immune repertoire, said Maeurer. "Since the thymus is activated, we have more barriers; we have more T cells available, which are able to recognize tuberculosis-infected cells. This may be a very, very important point, because the immune system may be exhausted after chronic, long-term tuberculosis infection."

The Use of Bone Marrow Cells in Treating TB[5]

Bone marrow cells offer an intriguing approach to the treatment of TB, said Gergert. To determine the feasibility of this approach, he and his colleagues have been studying the effects of bone marrow cell transplants on the growth of *M.tb.* in infected mice. For this study, they used an inbred, TB-susceptible strain of mice and bone marrow cells taken from TB-resistant mice. They then introduced a strain of *M.tb.* into the mice and measured their survival rate after infection under various experimental treatment protocols.

One group of mice received no treatment and served as a control. Three other groups received isoniazid therapy, isoniazid plus bone marrow cells, or just bone marrow cells. The isoniazid was administrated to the mice intragastrically 3 days after infection and then daily for 2 months. The bone marrow cells were introduced intravenously, also 3 days after infection and then once a week for 2 months.

Among the control group that received no treatment, all were dead within 25 days. The mice in all three treated groups survived throughout the experimental period. Thus, said Gergert, the transplant of bone marrow cells into infected mice significantly improved their survival rate with no other intervention. The life spans of these mice were comparable with those of the groups of animals that received chemotherapy or chemotherapy plus bone marrow cell transplants.

The introduction of bone marrow cells also significantly inhibited the growth of *M.tb.* in the organs of infected mice, although not quite as much as in the groups treated with isoniazid. In addition, the mice treated with bone marrow cells had higher levels of specific cell immunity, as measured by the delayed hypersensitivity reaction and interferon-gamma levels. Thus, the transplantation of bone marrow cells strengthened the anti-TB immune response, said Gergert.

[5]This section is based on the presentation of Vladislav Gergert, Central Scientific Research Institute of TB, Russian Academy of Medical Sciences.

7

TB and Drug-Resistant TB in Vulnerable Populations

Key Messages

- Pediatric TB is generally underreported since children can be difficult to diagnose and are often overlooked or slighted in TB statistics.
- Treatment of children calls for quality-assured pediatric formulations with standard regimens.
- Interventions in the lives of TB patients who suffer from alcohol or drug dependence can greatly reduce treatment default rates and the spread of drug-resistant strains.
- Despite an increase in HIV infection rates, the number of active TB patients in Russian prisons has fallen by more than half over the past decade, in part because of more effective diagnostic and treatment programs.

Speakers at the workshop addressed TB and drug-resistant TB among three particularly vulnerable populations: children, people with drug and alcohol dependencies, and the incarcerated.

DRUG-RESISTANT TB IN CHILDREN: THE HIDDEN EPIDEMIC[1]

Pérez-Vélez has been studying TB in the port city of Buenaventura, Colombia, since 2006. According to Pérez-Vélez, drug-susceptible and drug-resistant TB in children is underdiagnosed and underreported, and efforts to combat it are therefore underfunded. TB in children is a "hidden epidemic" and a major neglected child health problem he suggested, especially in communities that are ill equipped to address the problem adequately.

Data typically include only microbiologically confirmed and mainly smear-positive cases, yet children frequently have extrapulmonary TB, which can be difficult to diagnose clinically and confirm bacteriologically and carries its own set of complications. There are two additional reasons why accurate information on the epidemiology of TB in children is limited: (1) the criteria for defining a case of TB in a child vary, and (2) of the four WHO criteria for diagnosing TB in children, two (PPD-tuberculin test and radiography) often are not available in resource-limited settings—those with the highest burden of TB.

Furthermore, until 2007 WHO typically grouped all children in one age category—ages 0–14—rather than analyzing them in more precise subgroups. Even today, WHO reports results only for ages 0–4 and 5–14, even though children aged 5–10 tend to develop TB at much lower rates, thus confounding the latter grouping. In countries with an intermediate burden of TB, including many Latin American nations, many regions have high-burden pockets of TB; when averaged with the TB notifications from low-burden regions, however, the high-burden areas effectively disappear and consequently receive little attention. Native Indians (Amerindians) are an example of a highly vulnerable population, with some reservations having incidence rates as high as 1,000 per 100,000 population and high mortality. Another group underrepresented in surveillance reports consists of peasants, including many children, displaced by civil wars and often living in camps.

Children also have traditionally been excluded from surveillance of TB drug resistance. In the report series *Anti-Tuberculosis Drug Resistance in the World* (WHO, 2008), children originally were not included, and when they were, age groups between 0 and 14 were combined. In many health policy meetings and clinical training courses, pediatric TB is not even on the agenda.

Pérez-Vélez suggested that children be divided into different age groups and that a strong effort be made to eliminate underreporting. To advocate

[1]This section is based on the presentations of Carlos Pérez-Vélez, National Jewish Health and University of Colorado School of Medicine, Denver, Colorado; Dr. Shin; and Gary Reubenson, Rahima Moosa Mother and Child Hospital, South Africa.

effectively for policy changes, supporting data must be available to decision makers. In addition, Pérez-Vélez noted, quality-assured pediatric formulations of both first-line and second-line anti-TB medications are needed for standard regimens.

Drug-Resistant TB in Children in Colombia

Limited data from several Latin American countries reveal widely varying pediatric resistance rates (Table 7-1). Bogota, the capital of Colombia, has 8 to 10 million inhabitants. The incidence of TB is reported as 25 per 100,000 population, compared with an estimated 200 per 100,000 in Buenaventura (which is near Cali, the center of the Colombian drug trade). According to data gathered from 2001 to 2009 in Colombia, about 70 percent of children have pulmonary TB, and about a quarter have extrapulmonary TB. These pediatric patients also have a variety of TB clinical syndromes, including pulmonary, central nervous system, and lymph node diseases. Pérez-Vélez shared a current pediatric case he is treating, a 2-year-old girl with MDR TB adopted from China. The girl's strain of TB is resistant to a total of six drugs (although her case does not qualify as XDR TB). She has disseminated TB, including pulmonary disease (bronchopneumonia, endobronchial disease, bronchiectasis), with associated massive mediastinal

TABLE 7-1 Varying MDR TB Rates Revealed by Surveys of Anti-TB Drug Resistance in South American Children, 2001–2009

Country	Year(s) of Survey	Patients Tested	Any Resistance (%)	Isoniazid Resistance (%)	MDR (%)
Argentina	2005	N = 683	10.0	5.7	2.2
		P = 136	25.0	18.4	15.4
Colombia	2001–2009	N = 26	20.8	12.0	3.2
		P = 3	0.8	0.8	0.8
Paraguay	2001	N = 235	11.1	6.4	2.1
		P = 51	19.6	11.8	3.9
Peru	2006	N = 1,809	23.2	11.6	5.3
		P = 360	41.7	30.3	23.6
Uruguay	2005	N = 335	2.1	1.2	0
		P = 33	9.1	6.1	6.1

NOTE: N = new TB cases; P = previously treated TB cases.
SOURCES: Llerena et al., 2010; Wright et al., 2009.

lympohadenopathy (complicated by external compression of the trachea), two cervical lymphadenitis lesions, Pott's spinal disease, and severe failure to thrive. The armamentarium for treating this child is, as one would expect, quite limited, said Pérez-Vélez.

In Colombia in 2007, 593 cases of TB were reported in children below age 15, representing just 5.3 percent of the total number of cases in the country. This is a low number for an intermediate-burden country and should probably be closer to 10 percent, Pérez-Vélez noted. As a general rule, said Pérez-Vélez, 5–10 percent of the caseload in low-burden countries would be children, 10–20 percent in intermediate-burden countries, and 20–40 percent in high-burden countries, although these proportions are gross estimates based on epidemiological studies that carried out both passive and active case finding. In Buenaventura, a high-burden TB setting, the pediatric caseload was almost zero in 2006 and is now at 23 percent (personal communication, Cesar A. Moreira, TB Controller of Buenaventura). Also, about 45 percent of pediatric cases in Colombia were smear positive, which suggests a late diagnosis since children are generally paucibacillary and therefore smear negative and culture negative. This finding also suggests a dependency on smear microscopy-based, as opposed to culture-based, diagnosis, which is quite common in developing countries. In some countries, children diagnosed with TB (i.e., fulfilling the recommended WHO criteria) are not treated because of the misconception that they, like adults, require bacteriological confirmation. Pérez-Vélez suggested that a solely smear-based program is inadequate for bacteriological confirmation in children and that a strengthening of laboratory capacity (especially for mycobacterial cultures and associated drug susceptibility testing) is necessary.

Of 128 pediatric TB cases in Colombia from 2001 to 2009—although this clearly is an underreported number, said Pérez-Vélez—3 had been treated previously, and 125 were new cases. Of the new cases, 99 were drug-susceptible, 14 exhibited monoresistance, 8 exhibited polyresistance, and 4 were MDR TB. The accuracy of these results depends on having both accurate bacteriological tests and good-quality samples, Pérez-Vélez emphasized. Even in very young children (including infants), who cannot undergo the conventional specimen collection method of gastric aspiration/lavage, bacteriological confirmation (and subsequent drug susceptibility testing) can be carried out through nasopharyngeal aspiration after sputum induction. Pérez-Vélez's research group (Grupo Tuberculosis Valle-Colorado) is evaluating the bacteriological yield of alternative specimens to the gastric aspirate, including induced sputum, as well as a highly absorbent nylon string that absorbs the sputum swallowed by the pediatric patient over many hours while asleep or awake (known as the "string test"). Pérez-Vélez also stressed the importance of reducing the time elapsed between diagnos-

ing TB in children and obtaining results of drug susceptibility testing to guide the clinician in selecting an effective regimen of anti-TB medications.

Pediatric Drug-Resistant TB in Peru

Shin stated that in pediatric populations, patterns of drug resistance are often different from those in adults because pediatric TB infections are primary (i.e., transmitted from person to person). In these cases, excess morbidity and mortality are likely due to underdiagnosis. In Peru, a study examined 38 children with a median age of 11 who had experienced an average of more than 6 months from first TB diagnosis to MDR TB treatment. Rates of adverse events were much lower than for adults, and the children tolerated treatment very well despite the use of aggressive therapy. The median number of drugs in the regimen was six, and cure rates were 94 percent.

Pediatric Drug-Resistant TB in South Africa

An estimated 1 million cases of pediatric TB occur annually worldwide, three-quarters of which are in 22 high-burden countries, said Reubenson. Since the vast majority of these cases are smear negative, this figure is likely an underestimate. Pediatric TB has traditionally been neglected, suggested Reubenson. TB in children is difficult to diagnose and confirm, and from a public health perspective, children are less likely to transmit the disease. However, there is increasing awareness of the problem.

Children are especially important in assessing drug-resistant TB through surveillance programs because they represent patients that have recently been infected and therefore reflect circulating strains and prevalent drug susceptibility patterns. Yet international data on pediatric TB are extremely limited. In unpublished 2008 data, among 140 culture-confirmed pediatric cases in two Johannesburg academic hospitals, 49 percent were infected with HIV, 14.2 percent showed resistance to isoniazid, and 8.8 percent had MDR TB. Among this latter group, 85 percent had received no previous TB treatment, none had a history of contact with an adult with MDR TB, 30 percent had a history of contact with an adult with TB, 54 percent were infected with HIV, and the mortality rate was 30 percent (with a quarter of these deaths occurring prior to confirmation of MDR TB). Notably, none of those with confirmed MDR TB had a history of an adult MDR TB contact, and 85 percent had received no previous TB treatment. "These are the things we are taught to look for when trying to diagnose pediatric MDR TB," said Reubenson, "and they would not have been helpful in these situations."

Reubenson said he was aware of two confirmed cases of pediatric XDR

TB in Gauteng Province, where he works. Both had undergone multiple previous courses of TB therapy, and both were HIV-infected. One died, and one has had consistently negative sputa and is, it is hoped, cured.

Each South African province has its own treatment center for MDR TB, where cases are treated predominantly as inpatients. Isolates are tested for susceptibility to the second-line drugs ethambutol, ethionamide, streptomycin, amikacin, ofloxacin, and kanamycin, but not para-aminosalycylic acid, capreomycin, pyrazinamide, terizidone, or other quinolones. This series of tests largely follows national MDR TB treatment guidelines, but the Sizwe Hospital in Guateng Province does individualize therapy according to the specific isolates. Additional drugs used occasionally include high-dose isoniazid, clarithromycin, augmentin, moxifloxacin, para-aminosalycylic acid, and capreomycin. All HIV-infected children with drug-resistant TB receive ART, irrespective of clinical or immunological staging.

Almost no data are available on outcomes, although anecdotal experience indicates that outcomes are fairly good. As Reubenson suggested, however, patients who come to the hospital have in a sense "preselected" themselves for survival, so their prognosis would be expected to be better than that for the overall cohort.

MDR TB TREATMENT FOR PEOPLE WITH DRUG AND ALCOHOL DEPENDENCIES[2]

According to Shin, people who abuse alcohol have a higher risk of contracting TB, having drug-resistant TB, and experiencing excess morbidity and mortality. Researchers have looked at the ethnography of alcohol abuse in different settings, the role of alcohol in causes of death, and the effect of alcohol interventions on TB and alcohol dependency outcomes. One objective of these studies has been to integrate care for alcohol dependency into TB programs so that it is a part of TB management.

Shin noted that many patients who abuse alcohol are eager for treatment, despite the stereotype that they resist assistance. For example, two-thirds of eligible patients enrolled in a study of naltrexone therapy and counseling in Tomsk, even though the researchers initially suspected that alcoholic patients might not be willing or wish to receive care. Shin elaborated that these patients generally cannot afford counseling services through the private sector and are happy for the opportunity to receive treatment for their alcohol dependency during TB treatment. She suggested that, instead of viewing this population as untreatable, treatment programs must raise

[2]This section is based on the presentations of Dr. Shin and Piotr Golubchikov, Tomsk Regional Tubercular Clinic.

the level of support for these patients and become more aggressive in diagnosing and treating them.

Golubchikov presented a case study of treatment for patients with TB and alcohol dependency. Tomsk Oblast lies within the Siberian Federal District of the Russian Federation. It has a population of about 1 million living in an area of 317,000 square kilometers. The DOTS program was piloted in the Tomsk region of Russia in 1994 to treat drug-susceptible TB, and in 2000 the DOTS-Plus program was launched to treat MDR TB. Beginning in 2000, Partners In Health began working in Tomsk Oblast, and in 2004 the region received a grant from the Global Fund to Fight AIDS, Tuberculosis, and Malaria.

With financial support from Partners In Health, a cohort of patients was enlisted in MDR TB treatment from 2000 to 2002. Of 244 patients, 191 were cured, 16 failed, 12 died, and 25 defaulted. When 75 patients were enrolled in a second cohort for treatment in 2004–2005, the results were much worse (Figure 7-1). According to Golubchikov, the main reasons for the high failure and default rates in the second cohort were higher rates of alcoholism and drug addiction. This is especially unfortunate, said Golubchikov, because these patients tend to leave treatment facilities and infect others.

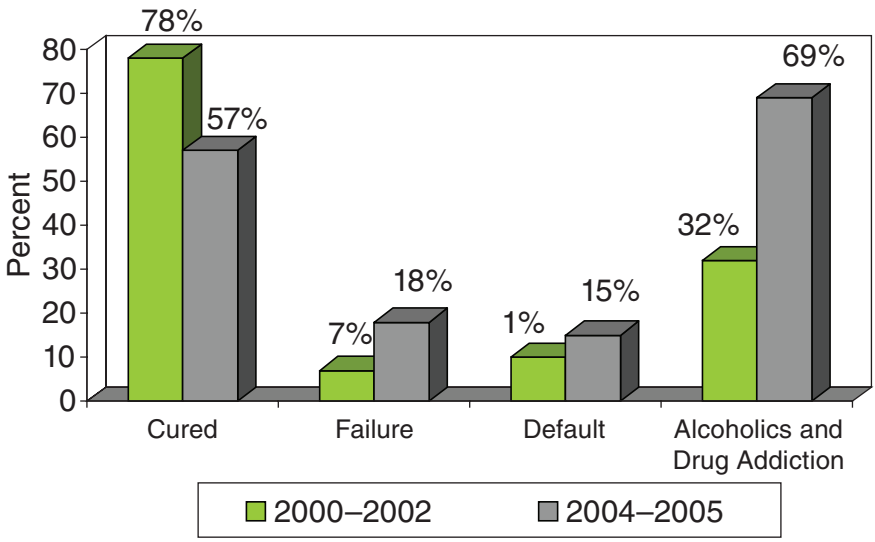

FIGURE 7-1 The 2004–2005 cohort had worse outcomes than the 2000–2002 cohort, largely because of alcoholism and drug addiction.
SOURCE: Golubchikov et al., 2010.

Golubchikov and his colleagues work mainly in the areas of alcohol harm reduction, narcotics harm reduction, social support for patients, development of patient-centered approaches, and training programs for staff and patients. All patients are tested for alcohol and drug dependence before beginning treatment.

If alcohol dependence is detected, patients receive counseling from a substance abuse professional and psychologist before they begin treatment, and this counseling is available throughout the course of therapy. The treatment program has been participating in research on the effectiveness of naltrexone to counter alcohol dependence. In addition, it provides separate counseling rooms for the substance abuse professional and the psychologist. Long-term communication with the psychologist is important to the treatment program, said Golubchikov.

For those dependent on drugs, counseling is available from a substance abuse professional and psychologist throughout the course of therapy. Outreach workers from Nasha Klinika, a nongovernmental organization, encourage intravenous drug users and MDR TB patients to receive treatment, and arrangements are made for patients to visit a drug abuse clinic to address their addiction or reduce their doses of drugs.

Patients receive a weekly distribution of food and other necessities, clothes, free travel to outpatient facilities, hot meals at local TB day-patient facilities, and the assistance of social workers for such tasks as applying for disability benefits. The development of patient-centered approaches included the expansion of day-patient facilities, with two hot meals served daily; home care for 60 patients; treatment at village health centers; and expansion of a network of volunteers in remote districts. The "Sputnik" program involves the provision of home visits for persistent or potential defaulters from TB treatment, with medical and psychological intervention and social support.

The Tomsk Oblast TB Service also has taken several administrative measures to counter MDR TB. A mobile default team visits the homes of patients who have missed their morning dose that day. A default committee consisting of a deputy head doctor, psychologist, substance abuse professional, and social worker meets to discuss patients who have missed their treatment for more than 3 days. A substance abuse professional, psychologist, and social worker conduct home visits. Improved case management and psychological support in the TB hospital have led to a decrease in early discharges of high-risk patients from inpatient clinics.

Health professionals receive training for clinical management of MDR TB, for detection and treatment of side effects, and for working with patients with alcohol and drug dependencies. Patients undergo their own health training, receive talks on TB, and have access to the management staff of TB facilities. Specialists from Alcoholics Anonymous and the Rus-

sian Orthodox Church are involved in the program to support TB patients. Also, patients who have successfully completed TB treatment programs talk with current patients.

These efforts have had a dramatic effect on the outcomes of MDR TB patients, said Golubchikov. In 2005, the year after the Global Fund grant was launched in Tomsk, defaults among civilian patients in the DOTS-Plus program dropped from 28.8 percent to 13.9 percent, and this percentage has continued to fall since then (Figure 7-2). The percentage of MDR TB among new bacteriologically proven cases of pulmonary TB investigated for drug susceptibility has fallen from a high of 16.8 percent earlier in the decade to slightly more than 13 percent. The level of XDR TB among all positive susceptibility tests has fallen from a high of 3.5 percent in 2006 to about 2.5 percent currently. TB mortality has declined more in Tomsk Oblast than in the Siberian Federal District and the Russian Federation (Figure 7-3). And the estimated reservoir of infectious MDR TB cases among the civilian sector has fallen from a high of more than 800 people in 2002 to fewer than 400 in 2009.

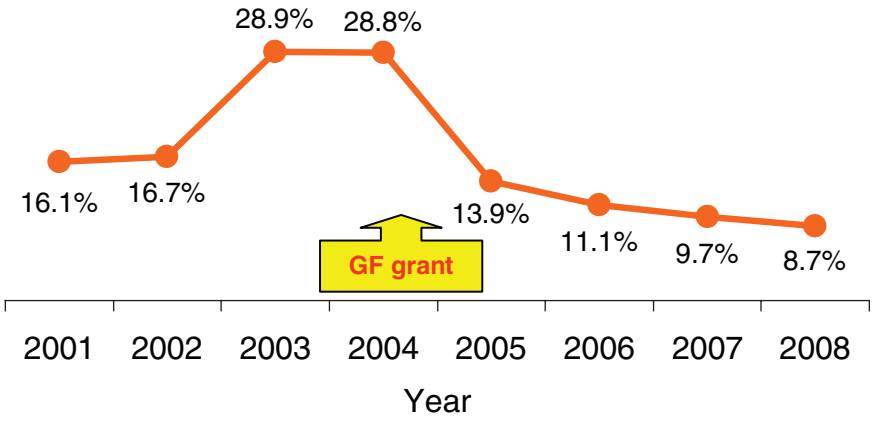

FIGURE 7-2 Default percentages among MDR TB patients dropped substantially after initiation of the DOTS-Plus program through a Global Fund grant.
SOURCE: Golubchikov et al., 2010.

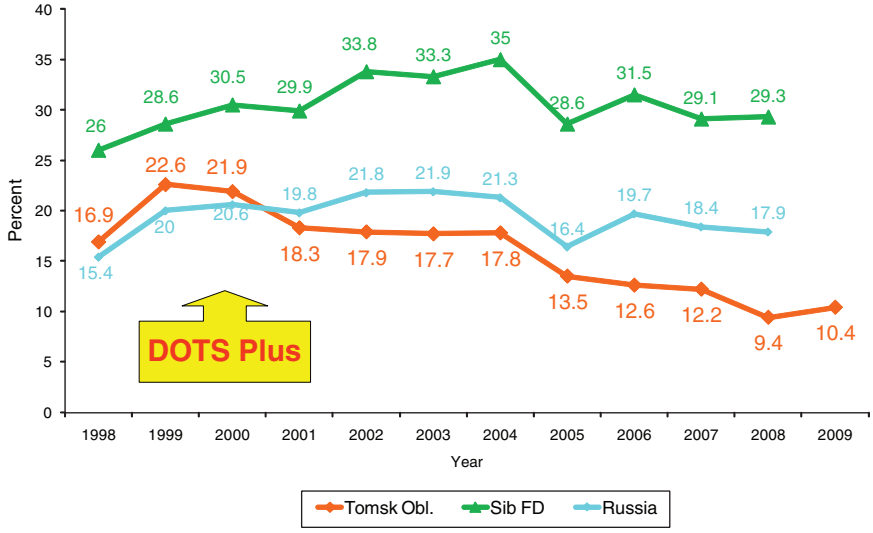

FIGURE 7-3 TB mortality in Tomsk Oblast has fallen at a greater rate than in the Siberian Federal District or the Russian Federation.
SOURCE: Golubchikov et al., 2010.

TB IN THE PRISON SYSTEM OF THE RUSSIAN FEDERATION[3]

Safonova reported that the number of active TB patients in Russia's penal institutions has fallen by more than half over the past decade (Figure 7-4). Even greater reductions have occurred in TB incidence and mortality in Russia's penal institutions. This decrease is due in part to shorter prison sentences following changes in criminal law, but it is also due to programs designed to detect and treat TB in the prison system. Financing from the Global Fund and The World Bank were used in part to create a laboratory network in the prison system, and 90 laboratories have been established. Drug sensitivity testing has allowed the detection of MDR TB cases followed by the introduction of second-line drugs. As a result, said Safonova, diagnostics are now quite good, with coverage rates of more than 97 percent, and prisons in 70 territories are now covered by second-line treatment.

During this same period, the number of HIV-infected patients in Russia's penal institutions has increased, as has the number of prisoners coinfected with HIV and *M.tb.* (Figure 7-5). The number of drug-resistant and MDR TB patients in Russia's penal institutions also has risen. In 2009, 54.4

[3]This section is based on the presentation of Svetlana Safonova, Russia's Federal Correction Service.

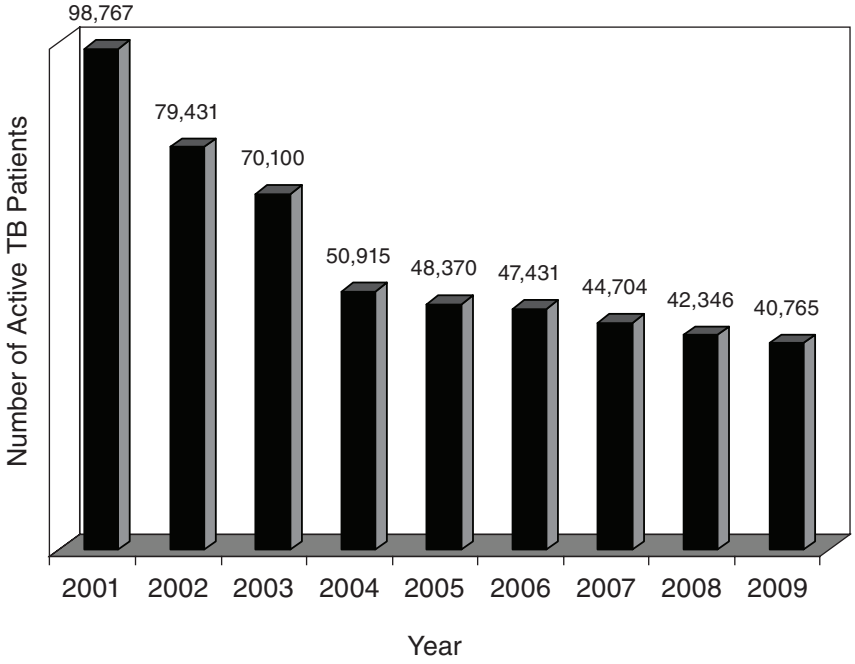

FIGURE 7-4 The number of active TB patients in Russia's penal institutions has declined over the past decade.
SOURCE: Safonova, 2010.

percent of patients exhibited drug resistance, and 21.9 percent had MDR TB. Among relapse TB patients, these percentages were much higher—82.9 and 49.9 percent, respectively. Among those TB patients in Russia's penal institutions that excreted *M.tb.,* 2.5 percent of new cases and 7.2 percent of relapse cases in 2009 were XDR TB.

Many new cases of TB are discovered only in penal institutions, meaning that the patients would not have known they were infected with TB if they had not been incarcerated. Of all new TB cases appearing in Russia, only 12 percent appear in penal institutions. About 90 percent of those TB patients diagnosed in penitentiaries did not know about their infection prior to arrest.

About 68 percent of these cases are occupants of urban areas, and only about 2 percent are homeless, contrary to a common stereotype, said Safonova. Among these new cases, 76 percent are aged 20–29, and the majority are employed. About 80 percent are unmarried, and 41 percent of those sick were convicted for the first time.

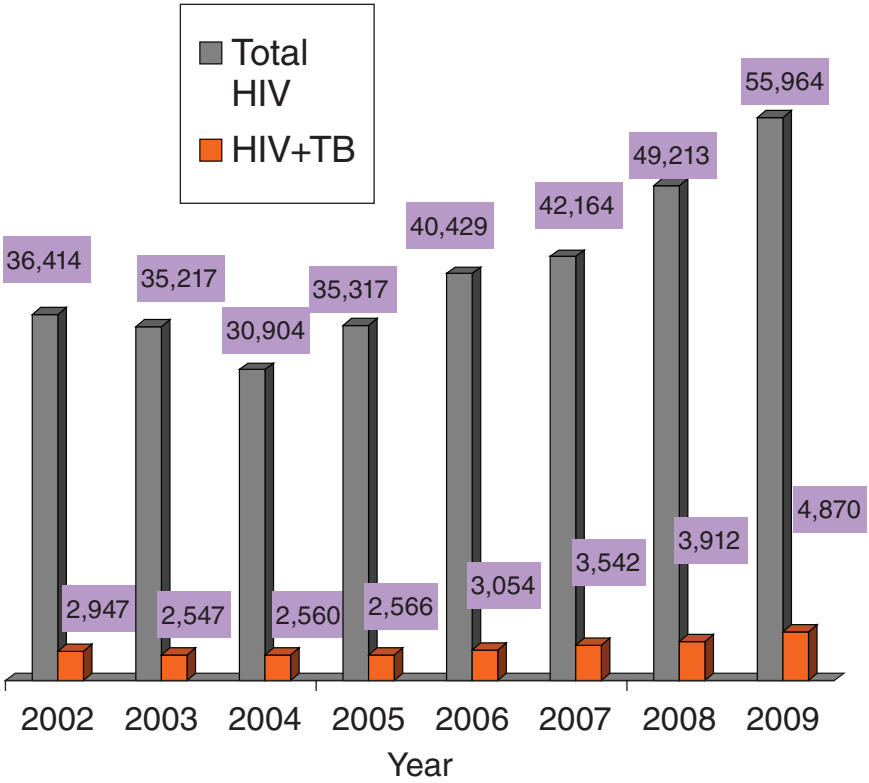

FIGURE 7-5 The number of patients infected with HIV and coinfected with HIV and *M.tb.* in Russia's penal institutions has risen since 2004.
SOURCE: Safonova, 2010.

The Russian penitentiary service has several priorities, said Safonova:

- early diagnosis of TB through x-ray and microbiological investigation,
- continued development of the prison service's laboratories and bacteriological investigation of all categories of TB patients,
- internal and external quality control of laboratories,
- continued development of the expertise of medical staff and provision of training, and
- continuing international cooperation.

8

The Second-Line Drug Supply Chain

Key Messages

- A paradigm shift is taking place with respect to the second-line drug supply chain—from reliance on the GLC mechanism to countries' assuming responsibility for the supply of quality drugs for their populations.
- Under a grant from the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Russian Health Care Foundation, in collaboration with the WHO and Partners In Health, has made many accomplishments in combating TB and MDR TB, including overseeing regular delivery of quality-assured second-line drugs.
- A partnership between Eli Lilly in the United States and Biocom in the Russian Federation led to Biocom's being prequalified for the production of cycloserine. If Biocom receives approval from WHO, it expects to supply drugs to countries that receive assistance from the Global Drug Facility program.

Presenters on the supply chain for second-line TB drugs described a new paradigm for the drug supply for drug-resistant TB and offered three different perspectives on MDR TB treatment and the drug supply chain in Russia.

A NEW PARADIGM FOR THE DRUG SUPPLY FOR DRUG-RESISTANT TB[1]

Major changes are now under way in the delivery and production systems for drugs needed to treat MDR TB, said Zintl. These changes will affect both the mechanisms and the patterns of supply for second-line drugs for MDR TB, and they represent a significant opportunity for national producers of reliable, high-quality anti-TB drugs.

The establishment of the GLC in 2000 represented a new paradigm in MDR TB care. As noted in Chapter 2, the WHO previously had counseled against treating patients with MDR TB in resource-limited settings. The fear at the time was that the effort to treat MDR TB patients would drain resources and distract attention from the more achievable goal of treating patients with drug-sensitive TB. The mandate for the GLC was to ensure that programmatic treatment was proper for MDR TB patients and that there was access to quality-assured second-line drugs at affordable prices. The GLC was also designed to enable, support, and monitor the Directly Observed Treatment Short course (DOTS)-Plus program. "The GLC was formed so that the new pilot projects did not increase the risk of MDR TB through poor-quality programs," said Zintl. "The committee controlled access and provided discounted prices for relatively limited supplies of quality-assured drugs." In 2006, WHO officially changed its policy to call for treatment of MDR TB patients in all countries with a significant MDR TB burden.

In the first 10 years of the GLC's existence, only about 20,000 MDR TB patients were treated in GLC-approved projects—an average of 2,000 patients per year. As the incidence of MDR TB rose, the GDF, which works on behalf of the GLC to supply second-line drugs, struggled to secure adequate quantities of these drugs. In addition, it became clear that acquired drug resistance is an increasingly serious problem (see Chapter 4). In many countries with high burdens of MDR TB, moreover, patients can and do acquire second-line drugs on their own or through medical providers who do not deliver the drugs under proper programmatic conditions. Market data show that sales of second-line drugs have been rising rapidly in countries with high burdens of MDR TB, as would be expected given the increase in the disease.

Under these circumstances, the paradigm of the GLC's approving projects one at a time for small numbers of patients began breaking down, said Zintl. This paradigm was leading to extensive delays and backlogs in the numbers of patients awaiting treatment because of a lack of drugs. It was posing a threat to multilateral funding for countries that could not access

[1]This section is based on the presentation of Paul Zintl, Partners In Health.

drugs from the GDF. And it was resulting in patients being placed on less-than-adequate regimens.

A major resolution adopted by the World Health Assembly in May 2009 marked a significant change in direction. The resolution identified MDR and XDR TB as threats to global public security. It noted that fewer than 3 percent of MDR TB cases were being treated according to WHO standards and with quality-assured drugs, and urged member states to achieve universal access to diagnosis and treatment of MDR and XDR TB.

Drug supply and quality were a major focus. The resolution noted that there had been inadequate demand from countries for high-quality or quality-assured drugs and that as a result, the supply of drugs available through the GLC had been limited. This inefficient drug market was a major bottleneck to treating patients with MDR and XDR TB, said Zintl.

The resolution urged member states to ensure that an uninterrupted supply of second-line drugs would be made available to patients. It stated that countries should make available a supply of drugs that meet WHO prequalification standards or strict national regulatory standards. The resolution also asked member states to help ensure that the drugs would be sold only by prescription and through registered providers and that fixed-dose combinations would receive priority. WHO is working on guidelines that will characterize strict national regulatory standards. However, the important change, said Zintl, is that countries now should accept this responsibility for themselves so that neither inadequate supplies of second-line drugs nor poor-quality drugs will continue to accelerate the spread of MDR and XDR TB.

The resolution requested that the WHO Director General help countries harmonize their national drug regulatory standards with international standards, thus enabling national pharmaceutical manufacturers to generate products of assured quality that can be sold in international markets. The Director General also is to work with countries on the development of quality indicators and to assist with monitoring and evaluation of the implementation of the measures called for in the resolution.

In this new environment, Zintl said, the role of the GLC is likely to evolve to that of monitoring and providing support and encouragement. The GLC will still monitor the risks of poor-quality implementation and drugs, but planning for the scale-up of MDR TB control has grown beyond the GLC's capabilities over the last 10 years. Brazil, India, and other countries will lead in this transition, Zintl suggested. "Brazil has been manufacturing quality drugs," he said, "albeit not WHO-prequalified, and treating large numbers of patients with these drugs for years. India is on the same path. China seems to be doing so as well. Other countries have an opportunity to follow that [lead]."

The risks of poor program implementation and poor-quality drugs are

still quite serious. Indeed, because of the magnitude of scale-up plans, these risks are even greater. Zintl expressed the hope that the GLC and WHO will create the necessary mechanisms to monitor these risks and encourage countries themselves to ensure proper program implementation and quality drugs.

National pharmaceutical companies now have an incentive to supply both domestic and international markets if they develop high-quality drugs and become prequalified, said Zintl. He emphasized the need for strong national and regional leadership in encouraging proper program implementation and high-quality drugs.

MDR TB TREATMENT AND THE DRUG SUPPLY CHAIN IN THE RUSSIAN FEDERATION[2]

Three speakers at the workshop discussed important aspects of the treatment of MDR TB in Russia. Goliaev described the efforts of the Russian Health Care Foundation to implement health care and social projects; Golubkov addressed the issue of ensuring a sufficient drug supply; and Potashnikov presented the perspective of a Russian pharmaceutical company.

Implementation of Health Care and Social Projects

A nongovernmental organization established in 1996, the Russian Health Care Foundation has completed projects representing investments of $400 million, including two leading World Bank projects implemented in Europe and Central Asia, Goliaev said. The foundation has been the principal recipient of an $88 million grant from the Global Fund to Fight AIDS, Tuberculosis, and Malaria to improve detection and treatment of TB and MDR TB, including TB in prisons; to build the capacity of partner organizations; and to improve HIV therapy in TB patients. Under this grant, it has trained thousands of specialists and instructors in the management of TB and has established a training and best practice center for disseminating good practices. It has provided equipment and supplies to laboratories and health care facilities and has supported the external evaluation of hundreds of TB diagnostic laboratories. The Russian Health Care Foundation, in collaboration with WHO and Partners In Health, helped territories receive GLC approval to treat MDR TB in 26 regional and 4 Federal TB Research Institutes, with approved projects using concessionally priced second-line

[2]This section is based on the presentations of Dmitry Goliaev, Russian Health Care Foundation; Alex Golubkov, Partners In Health; and Benjamin Potashnikov, Biocom, Russian Federation.

drugs. About $2 million was provided to five federal research institutes to strengthen the TB monitoring system, and the foundation supplied and helped repair equipment and software for prison hospitals and laboratories.

To build capacity among partners, the foundation has worked closely to implement the WHO program for combating TB in Russia. It provided financial support for 79 health facilities to establish diagnosis and reference units that provide counseling to TB and HIV patients before and after testing. It has helped write, publish, and disseminate more than 52,000 copies of training manuals, educational booklets, guidelines, and pamphlets on TB and HIV for all types of health care professionals. It also has held regional conferences on TB and HIV.

As part of an integrated approach to MDR TB therapy, the foundation has overseen the regular delivery of drugs for the full course of therapy and has worked to guarantee the quality of anti-TB drugs through Good Manufacturing Practices (GMP) certification and a multistage quality control process. One course of treatment under the GLC initiative costs $3,450 per patient, whereas it would cost 5 to 10 times more on the Russian market, according to Goliaev.

Patient therapy is carried out according to international protocols and is conducted under the direct observation of medical staff. The expected cure rate of MDR TB treatment is about 55 percent, said Goliaev. Patients receive social support to improve treatment adherence. Also, the Global Fund project helped improve infection control measures in many regions of Russia.

Problems facing the foundation include the increase in MDR TB patients, insufficient application of chemotherapy standards, late detection, insufficient patient compliance with treatment, a lack of monitoring for chemotherapy, and the ineffectiveness of initiatives to encourage sick people to undergo treatment. Only 68 percent of TB specialist posts are being filled, and current staffs are rapidly aging. As a result, the lack of qualified human resources is one of the problems in TB control in Russia today. There is also a lack of administrative support at the territorial government level.

To counter these problems, said Goliaev, the foundation is working to ensure adherence to treatment standards and observation of chemotherapy, is increasing social support programs to reduce treatment default rates, and is enhancing the quality of laboratory investigations. The goal, he said, is to provide quality-assured drugs, including second-line anti-TB drugs, on a continual and comprehensive basis.

Ensuring a Sufficient Drug Supply

Golubkov described the implications of recent policy changes for his organization. Partners In Health has been combating MDR TB in Tomsk

since 2000, prior to the establishment of the GLC. As noted by Goliaev, once the GLC had been instituted, drugs for MDR TB became available for just under $3,500 per year.

As Partners in Health began treating MDR TB in more sites around the world, drugs became more difficult to acquire; waits of 9 to 12 months were common. The prices for drugs then began to increase. For example, only one company, from Japan, was eligible to supply GLC-approved kanamycin, and that company was not registered in Russia. Partners In Health therefore had to turn to U.S. suppliers for kanamycin.

Another problem with importing drugs into Russia is that they must be approved by the humanitarian commission to be tax exempt; however, the commission conducts just a few meetings each year, which can slow down approvals. Golubkov expressed the opinion that this may become a bigger issue in the future.

With tens of thousands of new cases in Russia, Partners In Health will be unable to provide treatment to all of the people who need it. The reforms under way in the GLC should make it possible to avoid having a single supplier for a drug. Another step forward would be to establish a partnership between the regulatory authorities in Russia and international regulatory authorities. Still another option would be to increase the number of Russian companies qualified by WHO to be included on the list of producers of drugs and to supply them through the GLC.

All of these steps would improve the drug supply management system and make drugs more rapidly available, said Golubkov. In addition, he noted, Russia has a strong research capacity, and he suggested that the country should be involved in the search for new and more effective drugs against MDR TB.

Perspective of a Russian Pharmaceutical Company

Potashnikov explained how Biocom was prequalified for the production of cycloserine through collaboration with Eli Lilly. Biocom is a pharmaceutical manufacturer located in Stavropol in southern Russia. It was established in 1991 and upgraded in 2001, and since 2005 has been registered for the production of generic drugs.

In 2007 Eli Lilly transferred the technology for cycloserine production to Biocom, and together the two companies decided to take part in WHO's prequalification program for suppliers through the Global Drug Facility program. Consultations with WHO, in which Biocom received considerable help from WHO experts, proceeded through 2008. One complication has been the differing requirements of Russian authorities and WHO. In 2009,

Biocom submitted an application to the prequalification program, and the application was modified in response to review in early 2010.

If Biocom receives approval from WHO, it expects to supply drugs to countries that receive assistance from the Global Drug Facility program, including those receiving assistance from Partners in Health. By 2011 it hopes to have its drugs registered in many of the countries of the former Soviet Union and in other countries as well.

9

The Development of New TB Diagnostics and Drugs[1]

Key Messages

- The same principles that guided the successful response to the TB epidemic in New York City in the 1990s can guide the global effort against TB.
- Regulatory authorities play an essential role in the response against TB by assuring the quality of existing and new drugs and medical products.
- Regulatory science—the knowledge and tools needed to assess a product's safety, efficacy, quality, and performance—can serve as a link between biomedical research and safe and effective new medicines and therapies.
- Combination therapies, biomarkers, stem cell therapy, and pediatric TB therapies are examples of areas in which regulatory science will be critical to making rapid progress.
- Regulatory authorities need to work closely and continuously with academia, industry, and government agencies to inform strategies for data collection, identify emerging concerns, and promote research needed for regulatory decisions.

[1]This chapter and the key messages summarized at the beginning of the chapter are based on the presentation of Margaret Hamburg, U.S. Food and Drug Administration.

Russia has been an epicenter of the TB epidemic, said Hamburg, but it is also a country with an extraordinary tradition of science and medicine. Therefore, holding a workshop on drug-resistant TB in Moscow is both symbolically and substantively important. In her presentation, Hamburg provided a global overview of the challenge of developing new TB diagnostics and drugs. She then outlined the role of regulatory science and the need for collaboration in efforts to meet this challenge.

THE GLOBAL CHALLENGE

The numbers of TB cases during the New York City TB epidemic (see Box 2-3 in Chapter 2) appear small compared with the current numbers worldwide, Hamburg observed. Yet the same principles that guided the response in New York City apply globally. TB must be detected in all its forms as early as possible, which requires focused attention on at-risk populations and on a host of social, economic, and clinical variables. Health systems must be strengthened through bold policies, and financial barriers need to be addressed and overcome. Success in controlling the epidemic will depend on the ability to develop and distribute better tools with which to prevent, diagnose, and cure TB, as well as to ensure the quality and safety of those products throughout the supply chain and their life cycle, said Hamburg. Regulatory authorities have an essential role to play in all these areas.

First, regulatory authorities must assure the quality of existing and new drugs and medical products. This assurance is critical to achieving the benefits of treatment and avoiding the further development of resistance because of substandard medications. An example of efforts to that end is ongoing collaboration between the U.S. Food and Drug Administration (FDA) and regulatory colleagues in Russia.[2] Hamburg said that on the morning of her presentation at the workshop, she had met with her Russian colleagues to begin developing a blueprint for working together to share information and best practices. They also identified good clinical practice as a key area for partnership. A series of training workshops in that area will harmonize standards and approaches, which is particularly important as a growing body of clinical data emerges from Russian studies. In addition, opportunities for harmonization and standardization through such entities as the International Conference on Harmonization and other international

[2]The Statement of Intent on Collaboration between the U.S. Food and Drug Administration and the Federal Service on Surveillance in Health Care and Social Development of the Russian Federation (ROSZDRAVNADZOR) was agreed to on May 27, 2010. The agreement (Russian and English language versions) can be found at: http://www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/ucm217539.htm (accessed May 19, 2011).

bodies can strengthen the quality of medical products overall. Hamburg emphasized that assuring the safety and effectiveness of new medical products depends on having data from clinical trials that are conducted ethically and in accordance with internationally accepted practice.

New tools to combat TB need to reflect the best, most up-to-date science and technology possible, and in that respect, Hamburg suggested, there is reason for optimism. Yet much remains to be done. TB, especially drug-resistant TB, is underdiagnosed. Contributing factors are the neglect of laboratory services (see Chapter 5) and the failure to translate advances in scientific capabilities into new diagnostic technologies. Although progress has been made—the number of new TB diagnostic methods is growing, and methods now in development are promising—Hamburg pointed out that rapid, cost-effective, and easy-to-use diagnostics for both analysis of drug resistance and point-of-care diagnosis are still lacking (see Chapter 5).

Quite a few novel candidate TB drugs are in development, Hamburg observed. Five such drugs have entered clinical trials, with others in preclinical development (Global Alliance for TB Drug Development, 2010). Hamburg expressed the hope that two Phase III clinical trials, of 4-month drug regimens will be completed by 2012.

In addition, almost 30 vaccine candidates are in preclinical development. Eight have entered clinical trials, three of which are in Phase II studies. Thus, compared with a decade ago, there is "no shortage of innovation in the pipeline to prevent, diagnose, and cure TB," said Hamburg. Still, continued investments of money and scientific expertise will be necessary to sustain and extend this progress, she noted.

THE ROLE OF REGULATORY SCIENCE

Hamburg pointed to the special responsibility of regulators in ensuring that regulatory pathways are in place for the evaluation and approval of new products. Regulators must help identify the types of studies and data needed for rapid review and approval. Fulfilling this responsibility will require applying better science and more innovative approaches to drug development and medical product review, Hamburg said.

Regulatory science can serve as the link between cutting-edge science and technology and progress in the form of safe and effective new medicines and therapies. Regulatory science consists of the knowledge and tools needed to assess and evaluate a product's safety, efficacy, quality, and performance. It comprises an array of disciplines and approaches, including bench research, clinical research, epidemiology, bioinformatics, statistics, and bioimaging. "Regulatory science is not really about the science that is brought to the table by any one company or innovator to support an individual product," said Hamburg. "It's really [about giving] us the knowledge

and tools to address whole classes of important products. It requires the collaboration of government, industry, and academe to be effective." Using this knowledge and these tools, regulators can develop new methods, standards, and models that will speed the development, review, and approval of medical products and support optimal quality assurance.

A key challenge is translating the explosion of new knowledge and capabilities from many domains of research into real-world products and programs. According to Hamburg, regulatory science is an important part of the answer, yet it has been "underappreciated and underdeveloped." Continual developments in science and technology in fields as diverse as genomics, systems biology, stem cells, and nanotechnology hold promise for major therapeutic advances. In the area of stem cell therapy, for example, characterizing stem cells and ensuring their stability and purity could make it possible to make those new products available to patients. But the scientific community currently lacks the ability to translate many of these developments into vital products for those who need them. Hamburg emphasized the importance of closing this gap, and suggested that one means to that end is to streamline and modernize regulatory pathways.

To take advantage of the breakneck speed of scientific advances, innovation in regulatory science needs to be emphasized just as has innovation in biomedical research. An example is research into new treatments for drug-resistant TB. Curing drug-resistant TB requires multiple drugs over many months, and the development of resistance is a constant problem. Combination products could be much more effective, but the approval process for such products will be lengthy if each drug needs to be approved independently, followed by approval for their combination. As a result, the FDA has embarked on a new initiative to work with researchers and companies interested in developing combination products. This effort is scientifically complex for the agency, "but it is what patients need and what the public health demands," said Hamburg.

Another example involves the identification, characterization, and qualification of biomarkers. With serious or life-threatening diseases, surrogate endpoints based on epidemiologic, therapeutic, pathophysiologic, or other evidence can be used to predict clinical benefit. This approach has yielded great benefits in the case of HIV/AIDS. Appropriately selected and used, biomarkers can enhance the identification of candidates for drug discovery, support more efficient dose selection in early clinical research, and accelerate clinical trials. Hamburg emphasized the potential benefits of such approaches for TB. Last year, for example, an FDA advisory committee recommended the accelerated approval of new drugs for MDR TB on the basis of sputum culture conversion, which could reduce by years the time required for the delivery of new, more effective treatments to patients. In addition, biomarkers have great potential value for TB vaccine research

by enhancing the ability to evaluate the effectiveness of and response to candidate vaccines.

Finally, Hamburg stressed that assessments of existing and new treatments for TB should include children—both those with and without HIV infection—as well as formulations that are appropriate for pediatric populations. Multiple countries could benefit from studies that were well done and that addressed, from the beginning, critical data requirements for regulatory review and approval. Regulatory authorities could help by encouraging companies to pursue such efforts.

THE NEED FOR COLLABORATION

Success in the development of new TB diagnostics and drugs will depend on outreach and collaboration, said Hamburg. Regulators must be active participants in research and development through partnerships with academia, industry, and government agencies. Regulatory authorities should not be waiting at the end of the pipeline to see what emerges. They should be involved as product ideas are developed and as products go through the research and development process to inform strategies for data collection, identify emerging concerns, and ensure that advances in clinical trial analytics or biomarkers are being integrated into research activities. Regulatory authorities also have a responsibility to monitor drugs and other medical products once they enter the marketplace to ensure safety and appropriate use throughout the products' life cycle. Hamburg expressed her desire to see the FDA play an active role throughout the development of safe and effective tools to combat TB for the benefit of the American people and the world. Finally, she emphasized the importance of the sharing of clinical trial data across regulatory authorities to answer important questions of safety and efficacy.

10

Convergence of Science and Policy to Create a Call for Action

During the final session of the workshop, Salmaan Keshavjee, Gerrit Coetzee, Janet Tobias, Paul Farmer, Carlos Pérez-Vélez, Peter Cegielski, and Mingting Chen summarized the major themes that emerged from the presentations and discussion in the areas of key challenges, infection control, diagnostics, treatment, high-quality care for all, and linkages from science to clinical care.

KEY CHALLENGES

Keshavjee began by observing that the past decade has seen gains in policy, diagnostics, the extension of treatment to more patients, drug delivery mechanisms, and ambulatory care, but major gaps remain. More than 93 percent of patients do not receive treatment, and fewer than 1 percent are being treated with quality-assured drugs in programs of sufficient quality. The results from the PETTS (see Chapter 6) are particularly disturbing, he said, showing that many patients exhibit resistance to second-line drugs at baseline. In part, this finding reflects the fact that patients often seek care and take drugs periodically while they are awaiting treatment.

Data from South Africa and China confirm these high levels of drug resistance. The data from China showing 25 percent resistance to fluoroquinolones—the backbone of the second-line drug regimen—are startling, said Keshavjee. Coetzee observed that South Africa has been hit by multiple "avalanches," including the HIV epidemic, drug-resistant TB, and a rapidly migrating population. In response, the country has been deploying line probes to identify MDR TB patients early, but this effort has caused the

health care system in South Africa to be severely overburdened. In contrast, some of the data from Russia are promising, he said. TB has declined in prisons and in the civilian sector. Still, the total numbers of TB patients in the country are staggering.

The situation with respect to the treatment and diagnosis of children also remains stark, said Keshavjee. Representing 10–25 percent of patients, children demonstrate the complexity of the challenge, especially since diagnostics still cannot identify many cases of pediatric TB. Keshavjee emphasized the importance of making children a priority in the fight against TB.

The addition of MDR TB cases to the current pool of TB cases is cumulative, said Keshavjee. Patients are being diagnosed earlier and are being given effective treatment, but for that reason they also are present in the health care system longer. And because MDR TB is much more expensive to treat than drug-susceptible TB, budget pressures are severe.

Moreover, the data regarding amplification of resistance are compelling, according to Keshavjee. If the right regimen is not initiated from the beginning, resistance is amplified. A one-size-fits-all approach is not advisable given the existing data. But ensuring that people are receiving the treatment they require through tailored therapy will not be easy.

Finally, Keshavjee emphasized that TB is striking particularly hard in socially vulnerable populations, such as people who abuse alcohol (see Chapter 7). Delivering care to these populations is a daunting task, although it can be accomplished through careful planning.

Keshavjee cited PEPFAR as a model for what can be accomplished. In the case of PEPFAR, a disease was viewed as an emergency, resources were made available, boots were put on the ground, and outcomes were produced. These outcomes may not be perfect, but people are on treatment.

Coetzee stressed that countries need to strengthen their health systems to deal with the TB epidemic, but it is difficult for them to establish complex laboratory networks, multiyear treatment programs, monitoring of adverse effects, and so on. In South Africa in particular, for example, it is very difficult to scale up successful approaches with limited resources, especially limited human resources. Coetzee explained that money can usually be found without difficulty through such sources as PEPFAR; the biggest problem is finding and attracting the individuals to carry out the work.

Keshavjee suggested that the provision of technical assistance needs to change. Many places in the world require experts who can work with the local system for months to build up a health infrastructure, yet long-term onsite technical assistance is rare. Even New York, with a well-developed health system, required many inputs to counter TB.

INFECTION CONTROL

Keshavjee noted that infection control remains a major problem, as demonstrated by the data from Shanghai (see Chapter 4). Until patients are started on treatment, they are infectious. Information management also remains a problem in many places, with implications for both diagnosis and treatment (see Chapter 5). Systems to manage data and get results back to clinicians are still lacking in many places.

Keshavjee pointed to some positive developments with regard to infection control. In China, for example, a country with a complex health system and many patients, the fact that the government is combating TB is grounds for hope (see Chapter 2).

DIAGNOSTICS

Farmer noted that diagnostic methods are linked to both care and prevention. For example, a molecular diagnostic for rifampin resistance would be invaluable, since one mutation describes about 80 percent of rifampin resistance, and rifampin resistance stands as a marker for MDR TB. Yet such a diagnostic is not yet widely available, although Farmer commended the Russian TB community for working hard to improve the quality of diagnostics (see Chapter 3).

Current diagnostics are inadequate, said Farmer, and even recently introduced diagnostics have weaknesses. While the EXPAND-TB Program launched by the WHO through the Global Laboratory Initiative is an important step toward ensuring that countries have culture and rapid diagnostic capacity, much more is needed, including point-of-care tests. Some potential rapid diagnostic methods, such as the mass spectrometry approach, are very appealing, but it remains to be seen how practical they will be for TB.

Farmer noted that candidates for rapid diagnostics exist (see Chapter 5), but a push is needed to bring these candidates to the mainstream. Validation of tests needs to be transparent so that the international scientific community knows that they work. Regulations also must be established for the use of these tests. A forum for action could push new diagnostics forward so they would not linger from year to year without being ready for deployment, said Farmer.

TREATMENT

Keshavjee summarized problems in obtaining enough quality second-line drugs (see Chapter 8). Existing mechanisms for making high-quality second-line drugs available, such as the GLC, have many strengths. The

GLC system provides drugs at a great discount compared with local markets, especially in Russia, where GLC prices are 5 to 10 times lower. But the market for these drugs is limited in that it is a market for what people can buy, not what they need to buy. Partly as a result, delays are experienced through the Global Drug Facility mechanism. Challenges are experienced as well in individual countries, such as regulations that require buying drugs from domestic manufacturers. An increase in drug prices also has affected the number of patients being treated. For example, when the price of some of the GLC drugs sold through the Global Drug Facility rose by 44 percent, 1,000 patients had to be cut from treatment in Russia. The opposite is happening with HIV drugs, whose prices are declining.

Many countries have hundreds of thousands of people to treat. They must be able to buy drugs through their own mechanisms and from their own suppliers, and they must be able to ensure that their manufacturers are making quality products, said Coetzee. Single suppliers and manufacturers are not sufficient. Tobias emphasized that strengthening the regulatory authorities in countries with a high burden of MDR TB and in countries that export drugs is important as well.

Coetzee noted that in South Africa, the biggest policy debate currently involves treatment of MDR TB in the community. Health care systems are so overwhelmed, with hospitals being full and people being put on lists and sent home, that community treatment is already a reality. The group that has the most say in decisions about community treatment is the community itself, but the community "has not yet spoken," said Coetzee. TB is more stigmatized now than in the past, with drug-resistant strains circulating in the community. Civil problems need to be managed sensitively.

Community-based care cannot happen unless patients and communities are treated as partners in the health care system, said Tobias. Prevention, infection control, and treatment all require partnerships with patients and communities. Tobias noted that the development of partnerships in part requires finding advocates "because that will increase public will and funding." As the experience in Tomsk showed, even difficult patients can be partners (see Chapter 7). "They may be alcoholic, they may be challenged, but they are becoming our partners. That's why we are going to be successful," said Tobias.

HIGH-QUALITY CARE FOR ALL

People in affluent countries expect the best available care, while people in less affluent countries, and even children in affluent countries, are expected to be satisfied with lower-quality care. This double standard is based on the false rationale of inadequate resources, said Cegielski. The

proper response is not to lower the standards but to increase the resources. That such an outcome is possible has been demonstrated repeatedly over the past decade by the Global Fund to Fight AIDS, Tuberculosis, and Malaria, UNITAID, PEPFAR and other U.S. government contributions, the Gates Foundation, the increase in the NIH budget for TB research, and other funding decisions. Similarly, said Cegielski, it is not appropriate to accept policy guidelines and recommendations that promote lesser standards for people who live in less affluent circumstances, in middle-income countries, or in lower-income countries. The development of international standards for TB care and new initiatives for the improvement and acceleration of regulatory guidelines and frameworks demonstrate what is possible.

Farmer indicated that various dogmas and ideologies have hampered rather than enhanced responses to the epidemic. The main source of tension has been a real or perceived scarcity of resources, often taking the form of competition between people who are working on the same team—for example, on TB and on diabetes. Farmer said this type of competition is seen in all areas of medicine. However, "The more you go down this gradient of social inequality towards so-called resource-poor settings, the more this competition is palpable and, I would say, unhealthy."

The example of AIDS illustrates how this competition can be overcome, said Farmer. Twenty years ago, when he was an intern at Brigham and Women's Hospital, the wards were full of young adults dying of AIDS. By the time he had finished his training in infectious disease, combination chemotherapy had emptied the hospitals of patients with AIDS, and death rates had dropped dramatically. Another example of cooperation rather than competition involves mother-to-child transmission of HIV. In the early 1990s, a major epidemic of pediatric HIV in the United States was feared because there had been a substantial epidemic of HIV infection among women living in poverty. Yet in 2007, said Farmer, fewer than five American children died of AIDS. Although AIDS remains a leading killer of young adults, a combination of treatment for women in the United States and mandatory testing of women during pregnancy prevented a pediatric epidemic. Yet in South Africa, TB and HIV remain among the leading killers of children.

It is not a good idea to talk about diseases as untreatable, said Farmer. The tools may not yet be available for pan-resistant TB—patients cannot currently be cured when their infection is resistant to nine or ten drugs. But real or perceived scarcities can undermine the kinds of collaboration needed for prevention and care.

The world is undergoing a transition, said Pérez-Vélez. Many countries, including the former Soviet Union, have experienced changes in their public health systems as a result of overall changes in government. Health care has

undergone dramatic changes in South America, for example. Colombia has been moving toward a model of competing, managed-care organizations, which is a familiar model in the United States. Consequences of this change have been that BCG vaccinations have decreased, active case finding and contact investigation have been reduced, cure rates have decreased, and default rates have increased. All this has been the result, said Pérez-Vélez, of transferring TB control to the for-profit managed-care marketplace. "There is no profit to be made in tuberculosis, as we all know too well," he said. In the United States, the CDC and the states maintain good TB control programs, but the public–private mix has not thrived in many developing countries.

Pérez-Vélez concluded by calling attention to the International Standards for Tuberculosis Care (ISTC), which have been endorsed by more than 50 national and international organizations and are widely used in TB control programs. An independent body's monitoring of countries' adherence to the ISTC in both the public and private sectors could counter the lack of political will to uphold international standards of TB care, said Pérez-Vélez.

LINKAGES FROM SCIENCE TO CLINICAL CARE

According to Farmer, science has not kept pace with the epidemics of HIV and drug-resistant TB. The science is moving forward, but uptake into public health programs is slow everywhere in the world. This gap between knowledge and implementation is the biggest problem facing medicine in the United States, Farmer said, and in most of the places where he has worked. Cegielski echoed this point, saying that many new diagnostics are already commercially available, but they are not universally accessible. The chance that a new compound in the drug development pipeline will make it to final regulatory approval and the commercial market is only about 70 percent. So the question becomes what to do while waiting for necessary breakthroughs.

One possibility, said Cegielski, is to accelerate regulatory science, as Margaret Hamburg suggested (see Chapter 9). For example, the Critical Path Initiative is focusing on drugs in combination so that each new drug is not expected to solve the problem, because resistance inevitably will emerge.

Also, a great deal of work can be done with available tools, said Cegielski. Many drugs on the market that have been approved by the FDA and other regulatory authorities may have antimycobacterial activity. They could be investigated immediately for their efficacy against TB in general or drug-resistant TB in particular. Such tests also would help build the

infrastructure for clinical trials, for the evaluation of new drugs, and for the development of new diagnostics.

The vital links among clinical care, basic science, clinical research, drug manufacturing, and better policy require the kinds of collaborations forged at the Moscow workshop. "I hope this will be regarded by others as one in a series of potentially historic meetings that push forward the envelope as we contemplate improving our responses to drug-resistant tuberculosis," said Farmer.

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Appendix A

Agenda

THE NEW PROFILE OF DRUG RESISTANT TUBERCULOSIS: A GLOBAL AND LOCAL PERSPECTIVE

Sponsored by the U.S. National Academy of Sciences, Institute of Medicine, Forum on Drug Discovery, Development, and Translation, and the Russian Academy of Medical Sciences, this 2-day workshop will address the spread of multidrug-resistant (MDR) tuberculosis in Russia and across the globe, as well as the rapid emergence and spread of extensively drug resistant (XDR) tuberculosis. The implications of totally drug resistant (TDR) tuberculosis will also be discussed, as well as the newly emerging profile of MDR TB.

Objectives: The primary goals of this workshop are:

- to increase awareness and create a renewed sense of urgency of the growing global burden of multidrug- and extensively drug-resistant tuberculosis (MD/XDR TB) and its profile in Russia;
- to consider the magnitude of transmission of drug-resistant strains and options for transmission and infection control;
- to address the MDR TB burden in vulnerable populations, including pediatric cases, those co-infected with HIV, and substance abusers;
- to assess current treatment options and approaches to patient care, taking into account the unique needs of the population being treated;

- to discuss the supply of quality-assured second-line TB drugs and the pipeline for a new "cocktail" of TB drugs;
- to assess the current state of the art for rapid detection of drug resistance—and its implication for patient management; and
- to suggest policies to accelerate improvements in drug-resistant TB treatment and infection control.

Wednesday, May 26

Conference Venue: International Science & Technology Centre (ISTC)
Krasnoproletarskaya ulitsa, 32-34
127473 Moscow, Russia

09:00–09:30 **Welcoming Remarks and Overview of Conference Objectives**
Dmitry Orlov, *Russian Academy of Medical Sciences*
Mikhail Perelman, *Moscow Medical Academy*
Gail Cassell, *Eli Lilly and Company*

09:30–12:30 **Roundtable #1: Magnitude of the Burden of Drug Resistant Tuberculosis—Local and Global Perspectives**
Co-Chairs: Marina Yakimova, *Central TB Research Institute*
Jeffrey Drazen, *New England Journal of Medicine*

Global Status of MDR/XTR Tuberculosis, *30 min*
Salmaan Keshavjee, Chair, *Green Light Committee (GLC)*
Harvard Medical School

Epidemiology of TB in the Russian Federation, *30 min*
Marina Yakimova, *Central TB Research Institute*

Prevalence of Drug Resistance at the Initiation of Second-Line Drugs in Eight Countries, *30 min*
Peter Cegielski, *U.S. Centers for Disease Control and Prevention*

Profile of MDR/XDR in South Africa Based Upon Laboratory Data, *30 min*
Gerrit Coetzee, *National Health Laboratory Service, South Africa*

Current Status of Disease Burden and Programmatic Management of MDR/XDR TB in China, *30 min*
Mingting Chen, *Center for Disease Control and Prevention, China*

Roundtable Discussion, *30 min*

12:30–13:30 **Lunch**

13:30–15:30 **Roundtable #2: The Capability of Health Care Systems to Keep Up with the Spread of MDR TB**
Co-Chairs: Elena Skachkova, *Central Research Institute for the Organization and Informatization of Health Care, Moscow*
Dale Nordenberg, *Novasano Health and Science*

Monitoring System of MDR TB, *30 min*
Elena Skachkova, *Central Research Institute for the Organization and Informatization of Health Care, Moscow*

Surveillance Systems for TB Drug Resistance in China, *30 min*
Renzhong Li, *Center for Disease Control and Prevention, China*

Laboratory lnformation Barriers to MDR TB Control, *30 min*
Dale Nordenberg, *Novasano Health and Science*

Roundtable Discussion, *30 min*

15:30 – 15:45 **Break**

15:45 – 17:45 **Roundtable #3: Treatment of Drug-Resistant TB in Vulnerable Patient Populations**
Co-Chairs: Irina Vasilyeva, *Central TB Research Institute*
Janet Tobias, *Ikana Media*

Treatment of MDR TB, the CTRI Experience, *15 min*
Irina Vasilyeva, *Central TB Research Institute*

Approach to the Treatment of Children Infected with Multidrug-Resistant TB, *15 min*
Elena Ovsiankina,[1] *Central TB Research Institute*

HIV and MDR TB Co-Infection, *15 min*
Olga Frolova, *Federal Center of TB/AIDS Treatment*

MDR TB in Cases of Substance Abuse, *15 min*
Piotr Golubchikov, *Regional Anti-Tuberculosis Dispensary, Tomsk*

Epidemiology of TB in the Prison System of the Russian Federation, *15 min*
Svetlana Safonova, *Federal Correction System, Russian Federation*

Response Panel and Roundtable Discussion, *45 min*
Sonya Shin, *Harvard Medical School*
Carlos Pérez-Vélez, *National Jewish Hospital, Denver*
Gary Reubenson, *Rahima Moosa Mother & Child Hospital, South Africa*

17:45–18:30 **Gaps in TB Research: Meeting Report from the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)**
Barbara Laughon, *NIAID/NIH*
Alexandr Apt, *Central Institute for Tuberculosis, Moscow*

Opportunities for International Cooperation
Stuart Politi, *Civilian Research and Development Foundation*

[1]Unable to attend the workshop due to an emergency.

Thursday, May 27

Conference Venue: International Science & Technology Centre (ISTC)
Krasnoproletarskaya ulitsa, 32-34
127473 Moscow, Russia

08:30–10:10 **Roundtable #4: Rapid Methods for Determining Drug Resistance in Tuberculosis and Implications for Patient Management**

Co-Chairs: Elena Larionova, *Central TB Research Institute*
Jerrold Ellner, *Division of Infectious Diseases, Boston University*

Molecular and Genetic Methods of Mycobacteria Identification in Russia, *20 min*
Tatiana Smirnova, *Central TB Research Institute*

Overview of Rapid Methods for Determining Drug Resistance in *Mycobacterium tuberculosis*, *20 min*
Elena Larionova, *Central TB Research Institute*

Implication of Rapid Detection of Resistance in Patient Management, *20 min*
Danila Zimenkov, *Engelhardt lnstitute of Molecular Biology, Moscow*

Response Panel and Roundtable Discussion, *40 min*
Maria Giovanni, *National Institute of Allergy and Infectious Diseases, National Institutes of Health*
Nico Gey van Pittius, *Stellenbosch University, South Africa*
Qian Gao, *Shanghai Medical College, China*

10:10–12:00 **Roundtable #5: MDR TB Transmission and Infection Control**

Co-Chairs: Rostislav Mitrofanov, *Novosibirsk Tuberculosis Research Institute*
Edward Nardell, *Harvard Medical School*

Infection Control in Anti-Tuberculosis Institutions, *20 min*
Elina Sevastyanova, *Central TB Research Institute*

Transmission of MDR/XDR in Shanghai, *20 min*
Qian Gao, *Shanghai Medical College, China*

Transmission-Based Genetic Analysis in South Africa, *20 min*
Nico Gey van Pittius, *Stellenbosch University, South Africa*

Turning off the Spigot: Reducing Nosocomial Drug-Resistant TB Transmission, *20 min*
Edward Nardell, *Harvard Medical School*

Roundtable Discussion, *30 min*

12:00–13:00 **Lunch**

13:00 – 13:50 **Roundtable #6: lnnovative Efforts to Advance MDR TB Control and Treatment**
Co-chairs: Vladislav Gergert, *Central SRI of TB, RAMS*
Jeffrey Drazen, *New England Journal of Medicine*

Stem Cell TB Therapy Application in Experiment, *20 min*
Vladislav Gergert, *Central SRI of TB, RAMS*

Stem Cell Therapy in MDR TB Patients: A Promising Approach? *20 min [via online presentation]*
Mark Maeurer, *Karolinska Institute*

Roundtable Discussion, *10 min*

13:50–14:35 **Roundtable #7: Addressing Challenges in MDR TB Drug Procurement**
Co-chairs: Nikita Afanasiev, *USAID, Moscow*
Paul Zintl, *Partners In Health*

The World Health Assembly Resolution on MDR/XDR TB: Is It Important for Russia's Second-Line TB Drug Supply? *15 min*
Paul Zintl, *Partners In Health*

Response Panel and Roundtable Discussion, *30 min*
Dmitry Goliaev, *Russian Health Care Foundation*
Alex Golubkov, *Partners In Health*
Benjamin Potashnikov, *Biocom, Russia*

14:35–15:00 **Break**

15:00–18:15 **Roundtable #8: Closing Plenary Lectures: A Blueprint for Action**
Chair: Gail Cassell, *Eli Lilly and Company*

Remarks from Academician Mikhail Perelman, *Moscow Medical Academy*

The Realities of Global MDR TB Control and the Growing Number of Totally Resistant Cases (XDR TB): An Argument for Quantifying the Threat in Tangible Ways
Paul Farmer, *Partners In Health*

The Critical Role of Regulatory Science and Innovation in Making Existing Drugs Matter and in Development of New TB Drugs and Diagnostics
Margaret Hamburg, *Commissioner, U.S. Food and Drug Administration*
Former Public Health Commissioner, New York City

Summary of Meeting Highlights and a Blueprint for Action
Salmaan Keshavjee, *Green Light Committee (GLC) Initiative*

Response Panel and Roundtable Discussion
Peter Cegielski, *U.S. Centers for Disease Control and Prevention*
Mingting Chen, *Center for Disease Control and Prevention, China*
Gerrit Coetzee, *National Health Laboratory Service, South Africa*
Janet Tobias, *Ikana Media*

18:15–18:30 **Closing Remarks**
Gail Cassell, *Eli Lilly and Company*

Appendix B

Summary of a Meeting of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Held May 24–25, 2010, Moscow, Russian Federation

During the workshop, Barbara Laughon of the National Institute of Allergy and Infectious Diseases summarized a meeting on research opportunities in TB drug discovery and diagnostics held on the 2 days before the workshop. The goals of that meeting, said Laughon, were to exchange information among researchers from the United States, Europe, Russia, China, and other countries and explore opportunities for collaborative research. Laughon focused in particular on how to increase cooperation among countries. The following are highlights of the discussions at the meeting:

- Russian Federation scientists are highly active in important areas of TB research, and multiple institutions are engaged in drug discovery, diagnostic, immunological, and pathological studies on TB.
- Sophisticated molecular diagnostics for MDR TB have been developed. However, these diagnostics are not necessarily available at the point of care.
- MDR and XDR TB strains are highly prevalent in Russia, but drug susceptibility testing for second-line drugs, as in the rest of the world, has yet to be standardized.
- Improved sensitivity of TB detection in HIV-positive individuals is needed.
- Differentiating between non-TB mycobacteria and *Mycobacterium tuberculosis* at the point of care can be difficult, leading in some cases to inappropriate treatment.

- Diagnostics and treatment regimens formulated for pediatric TB patients generally are not available.
- Support for basic science contributing to drug discovery is lacking. Improved connections among medicinal chemists, microbiological laboratories, and clinical investigators could hasten drug discovery.
- Facilities for the biosafety level-3 laboratories needed for some MDR TB research in Russia are limited.
- The TB strains used as standards in the West differ somewhat from those used as standards in Russia. These differences should be considered in comparing results of tests of diagnostics and drug effectiveness.
- Diagnostic drug susceptibility testing needs to be harmonized across Russia and, in particular, with new drug developers.
- Increased communication and collaboration among investigators within and outside of Russia could be beneficial to all participants. For example, the importation of reagents, equipment, and microbes is currently a barrier to collaborative research.
- Research opportunities supported by the National Institutes of Health and other organizations are open to Russian investigators.
- The clinical trial infrastructure needs to be strengthened for registration studies.
- Regulatory and bureaucratic bottlenecks need to be removed for chemical entities in Phase I and Phase II clinical trials.
- Standards of care and approaches to TB treatment need to be harmonized for multicenter trials.
- Present clinical sites in Russia and other nations need to be sustained and supported for forthcoming global Phase III trials.

Appendix C

Participant Biographies

Gail H. Cassell, Ph.D., most recently held the position of Vice President, Scientific Affairs, and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company, Indianapolis, Indiana. She is former Charles H. McCauley Professor and Chair of the Department of Microbiology, University of Alabama Schools of Medicine and Dentistry at Birmingham, a department that ranked first in research funding from the National Institutes of Health (NIH) during the decade of her leadership. She obtained her BS from the University of Alabama in Tuscaloosa and in 1993 was selected as one of the top 31 female graduates of the twentieth 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 past President of the American Society for Microbiology (the oldest and single largest life sciences organization, with a membership of more than 42,000). She was a member of the NIH Director's Advisory Committee and of the Advisory Council of the National Institute of Allergy and Infectious Diseases. She was named to the original Board of Scientific Counselors of the Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), and served as chair of the board. She recently served a 3-year term on the advisory board of the Director of CDC and as a member of the Secretary of Health and Human Services' Advisory Council of Public Health Preparedness. Currently she is a member of the Science Board of the U.S. Food and Drug Administration (FDA). Since 1996 she has been a member of the U.S.–Japan Cooperative Medical Science Program, responsible for advising the respective governments (U.S. State Department/Japanese Ministry of Foreign Affairs) on joint research agendas. She has served on several edito-

rial boards of scientific journals and has authored more than 250 articles and book chapters. Dr. Cassell has received national and international awards and an honorary degree for her research in infectious diseases. She is a member of the Institute of Medicine (IOM) and is currently serving a 3-year term on the IOM Council, the institution's governing board. Dr. Cassell has been intimately involved in the formulation 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 participant 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 (LCME), the accrediting body for U.S. medical schools, as well as other national committees involved in establishing policies on training in the biomedical sciences. She recently completed a term on the Leadership Council of the School of Public Health of Harvard University. Currently she is a member of the Executive Committee of the Board of Visitors of Columbia University School of Medicine, the Executive Committee of the Board of Directors of the Burroughs Wellcome Fund, Research!America, and the Advisory Council of the Johns Hopkins School of Nursing.

Peter Cegielski, M.D., M.P.H., received his bachelor's degree with honors from Harvard University in 1978. He received his medical degree in 1984 from the University of California, San Diego School of Medicine. He completed a residency in internal medicine in 1987 and a fellowship in infectious diseases/international health in 1990, both at Duke University Medical Center. For two years he was posted to Muhimbili Medical Center, University of Dar es Salaam, Tanzania, where he was a lecturer and consultant physician. After returning to the United States, Dr. Cegielski joined the faculty of the Division of Infectious Diseases/International Health at Duke, and in 1995 he received a master's degree in epidemiology from the University of North Carolina at Chapel Hill School of Public Health. From 1994 to 1996, he was at the University of Texas Health Science Center in Tyler, where he was an assistant professor of medicine and head of the TB service. At the end of 1996 he took a faculty position at the Johns Hopkins University School of Public Health, where he was field director of the HIV/AIDS research program at Chiang Mai University, Chiang Mai, Thailand. In 1998 he joined the International Activity of the Division of TB Elimination at CDC in Atlanta. In 2001, he was promoted to team leader for drug-resistant TB, his current position. Dr. Cegielski was a founding member of the STOP TB Green Light Committee for increasing access to

treatment of MDR TB and served as its chairman, 2004–2006. His work focuses on the epidemiology, prevention, diagnosis, and treatment of TB, especially drug-resistant TB.

Dr. Mingting Chen specializes in TB control and prevention. He received a master's degree from Peking Union Medical College and a bachelor's degree from Shanghai Medical University. Since September 2005, Dr. Chen has served as researcher/vice director with the National Centre of Tuberculosis Control and Prevention of China.

Dr. Gerrit Coetzee is a pathologist currently living in Johannesburg, South Africa. He is head of the National Tuberculosis Laboratory at the National Institute for Communicable Diseases, a division within the National Health Laboratory Service of South Africa. His main interests include anti-TB resistance within national program settings—particularly MDR and XDR TB, the epidemiology of TB in high-burden settings, molecular epidemiology and outbreak investigations, and surveillance of TB (especially MDR/XDR TB). He is currently managing a large 2-year line probe assay (LPA) roll-out project in South Africa, aimed at the very early detection of MDR TB and early initiation of optimal treatment.

Jeffrey M. Drazen, M.D., was born and raised in St. Louis. Dr. Drazen majored in physics at Tufts University and graduated from Harvard Medical School in 1972. After serving his medical internship at Peter Bent Brigham Hospital in Boston, he joined the pulmonary divisions of the Harvard hospitals. He served as chief of pulmonary medicine at the Beth Israel Hospital, chief of the combined pulmonary divisions of the Beth Israel and Brigham and Women's Hospitals, and then as chief of pulmonary medicine at Brigham and Women's Hospital. Through his research, Dr. Drazen defined the role of novel endogenous chemical agents in asthma, leading to four new licensed pharmaceuticals for asthma, with millions of people on treatment worldwide. In 2000, he assumed the post of editor-in-chief of the *New England Journal of Medicine*. During his tenure, the *Journal* has published major papers advancing the science of medicine, including the first descriptions of severe acute respiratory syndrome (SARS) and modifications in the treatment of cancer, heart disease, and lung disease, and has been at the forefront of the worldwide effort to register all clinical trials. The *Journal,* which has more than a million readers every week, has the highest impact factor of any journal publishing original research.

Jerrold J. Ellner, M.D., is professor and chief of infectious diseases at Boston University School of Medicine and Boston Medical Center. He has studied the immunopathogenesis of TB and TB in HIV through research

collaborations in Uganda and Brazil. Dr. Ellner has conducted clinical trials of the prevention and treatment of TB, as well as the first HIV/AIDS vaccine trial in Africa. His research group was the first to show that TB accelerated the course of HIV infection by activating viral replication in latently infected cells. Dr. Ellner was one of the principal architects of the Uganda–Case Western Reserve University Research Collaboration; a founding member of the Academic Alliance for AIDS Prevention and Care in Africa, which developed the Infectious Diseases Institute at Makerere University; and founding director of the TB Research Unit at Case Western Reserve University. He currently is principal investigator for an International Collaboration for Infectious Diseases Research program in Brazil and the TB Clinical Diagnostics Research Consortium. Dr. Ellner has authored more than 250 publications on TB and has trained a number of current academic leaders in infectious diseases.

Paul Farmer, M.D., Ph.D., is a medical anthropologist, physician, and founding director of Partners In Health (PIH), 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, Peru, Russia, Rwanda, Lesotho, and Malawi 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 PIH colleagues, the Hilton Humanitarian Prize. He is a member of the IOM and of the American Academy of Arts and Sciences.

Olga P. Frolova, M.D., Ph.D., is head of the TB/HIV Health Care Center, Ministry of Health and Social Development of the Russian Federation. In 1998 she defended her doctoral dissertation titled "Peculiarities of Tubercu-

losis in HIV-Infected Patients and Its Prevention." Dr. Frolova is chairman of the thematic working group of Russia's Health Ministry and WHO's Tuberculosis and HIV-Infected Patients.

Qian Gao, Ph.D., is a professor at Shanghai Medical College, Fudan University. He received his Ph.D. from the University of Southern California and was a postdoctoral fellow in the School of Medicine at Stanford University. Dr. Gao's research focuses on the molecular epidemiology of TB, especially the transmission regularity of this disease in China; the genetic diversity and pathogenesis of Beijing genotype strains of *Mycobacterium tuberculosis*; and biofilm formation of *Staphylococcus epidermidis*.

Nico C. Gey van Pittius, Ph.D., is an associate professor in biomedical sciences and a core member of the Department of Science and Technology/National Research Foundation, Centre of Excellence in Biomedical Tuberculosis Research, based in the South African Medical Research Council's (MRC's) Centre for Molecular and Cellular Biology in the Division of Molecular Biology and Human Genetics of the Department of Biomedical Sciences in the Faculty of Health Sciences of Stellenbosch University. A molecular biologist by training, he holds a B.Sc., Honns. B.Sc., M.Sc., and Ph.D. and recently completed his LLB. He also holds a certificate in intellectual property law. Dr. Gey van Pittius's research focuses on TB. Over the last 12 years, he has aimed to decipher the secrets of the genus *Mycobacterium*, with specific focus on the evolution of the mycobacteria and of mycobacterial pathogenicity and drug resistance. This work entails discovering how the mycobacteria developed to be successful pathogens, focusing on the mechanisms of evolution and the development of pathogenicity and resistance. Dr. Gey van Pittius's broader research interests encompass mycobacterial molecular epidemiology, drug resistance, and strain diversification. His work has been at the forefront of TB research and has led to the challenging of dogmas and the opening of new avenues of research toward understanding the evolution of mycobacterial virulence. Dr. Gey van Pittius is rated as a Y1 category researcher by the National Research Foundation, and he has received numerous honors, awards, and grants, including the Stellenbosch University Faculty of Health Sciences Award for Excellence in Research in 2008. He is a member of the Senate, the Health Research Ethics Committee, the Faculty Board, and the Committee for Postgraduate Research of the Faculty of Health Sciences of the University of Stellenbosch. He is also a member of several review committees and forums and belongs to numerous scientific societies, such as the American Society for Microbiology and the International Union Against Tuberculosis and Lung Disease. He is an elected member of the Academy of Science of South Africa (ASSAf) and the South African Academy of Science and Art. Dr. Gey

van Pittius has coauthored 50 papers and book chapters on various aspects of TB and is coinventor of two granted and three provisional patents in the field. His work on TB has been presented in oral and poster form at more than 35 international and more than 50 national conferences and meetings, and he has been invited to present lectures at numerous institutions worldwide. Dr. Gey van Pittius strives to promote the establishment of a vibrant scientific community encompassing both academia and industry, working together to ensure that South Africa becomes a leader in science and technology on the continent and globally.

Maria Y. Giovanni, Ph.D., holds a B.A. in biology and a Ph.D. in molecular biology from the University of Pennsylvania. She did her postdoctoral training in the NIH laboratory of Dr. Marshall Nirenberg in molecular neuroscience. She continued at NIH in 1988 at the National Eye Institute as director of fundamental retinal processes and then chief, Retinal Diseases Branch, and also led efforts in ocular genomics. In 2000 she moved to NIAID as assistant director for microbial genomics and advanced technologies. She has been involved in leading and coordinating efforts in infectious diseases, biodefense, influenza genomics/proteomics/bioinformatics/systems, biology resources and initiatives, and medical diagnostics for NIAID.

Dmitry A. Goliaev has been the Global Fund to Fight AIDS, Tuberculosis, and Malaria project director for the Russian Health Care Foundation (RHCF) since 2003. Prior to joining RHCF, he provided consulting services in the import/export of raw materials and manufactured goods, as well as expertise in the negotiation of credit agreements with Russia and foreign banks. Goliaev has also worked in a number of positions for the Moscow foreign trade association Technostroyexport, including deputy general director (1997–2002); chairman, board of directors (2000–2002); deputy director (1991–1997); head of the Business and Juridical Group (1987–1991); and senior engineer (1982–1987). His work with Technostroyexport involved the operational management of international import/export plans; currency flows and tax payment planning; and management of agreements between international banks and foreign partners, including the preparation and implementation of international contracts, the organization of procurement and supply, and the provision of payments for delivered goods and services. Goliaev received a degree in mechanics, with honors, from the Moscow Institute of Rail Road Engineering (1975) and a degree in international economic cooperation, with honors, from the All-Union Academy of Foreign Trade in Moscow (1982).

Dr. Piotr Golubchikov has been assistant to the head physician on medical work in Tomsk Regional Tubercular Clinic since 2006. He is responsible

for the treatment of MDR TB patients at the outpatient stage in the Tomsk region through grants from the Global Fund (2004–2009, 2010–2015). Dr. Golubchikov studied at Siberian State Medical University from 1994 to 2000, passing his clinical internship on TB and illnesses of the lungs in 2002. Before taking his current position at the Tomsk Regional Tubercular Clinic, Dr. Golubchikov worked for the Red Cross managing patients sick with TB.

Alexander Golubkov, M.D., M.P.H., currently serves as medical director for Russia and Kazakhstan for PIH. He supervises all medical and program activities for PIH projects in Russia and Kazakhstan, including medical care for multidrug-resistant TB, training programs, research activities, and grant implementation. Dr. Golubkov coordinates physicians, researchers, and project staff from Russia, Kazakhstan, and Boston based in PIH offices and at the Division of Global Health Equity at Brigham and Women's Hospital, where he holds a clinical appointment as an associate physician. As medical director, Dr. Golubkov integrates Russian clinical activities with other PIH projects and collaborates with partner organizations, such as the World Health Organization (WHO), CDC, the Global Fund, the U.S. Agency for International Development (USAID), and other agencies working on TB and HIV in the former Soviet Union. Dr. Golubkov holds a medical degree from the Novosibirsk Medical School and a master of public health degree from the Boston University School of Public Health. Before his appointment as medical director, he served as a Russian project manager at PIH/Boston. Before joining the Boston team, he worked for a PIH Russian project in Tomsk, where his primary responsibilities were managing the implementation of a $10.8 million Global Fund grant for Tomsk territory (a Russian territory with a population of 1 million), serving as a liaison with international partners and donors, supervising clinical work, and coordinating and managing the monitoring and evaluation component of the Global Fund grant. Before joining PIH, Dr. Golubkov served as a medical doctor at the Novosibirsk Institute for Cardiac Surgery.

Margaret Hamburg, M.D., was confirmed on May 18, 2009, by a unanimous Senate voice vote to become the 21st commissioner of food and drugs, a position for which she is exceptionally qualified by her training and experience as a medical doctor, scientist, and public health executive. Dr. Hamburg graduated from Harvard Medical School, and completed her residency in internal medicine at what is now New York Presbyterian Hospital-Weill Cornell Medical Center. She conducted research on neuroscience at Rockefeller University in New York; studied neuropharmacology at the National Institute of Mental Health, NIH; and later focused on AIDS research as assistant director of NIAID. In 1990, Dr. Hamburg joined the

New York City Department of Health and Mental Hygiene as deputy health commissioner and within a year was promoted to commissioner, a position she held until 1997. During her tenure, she carried out significant public health measures despite severe budget constraints while holding academic positions at Columbia University School of Public Health and Cornell University Medical College. Dr. Hamburg's accomplishments as New York's top public health official included improved services for women and children, needle-exchange programs to reduce the spread of HIV, and initiation of the first public health bioterrorism defense program in the nation. Her most celebrated achievement, however, was curbing the spread of TB. Dr. Hamburg confronted the problem by sending health care workers to patients' homes and taking other steps to ensure that they completed the drug regimen. Thanks to this program, the TB rate in New York City fell by 46 percent overall and 86 percent for the most drug-resistant strains within 5 years. Dr. Hamburg's innovative approach has become a model for health departments worldwide. In 1994, Dr. Hamburg was elected to membership in the IOM, one of the youngest persons to be so honored. Three years later, at the request of President Clinton, she accepted the position of assistant secretary for policy and evaluation in the U.S. Department of Health and Human Services (HHS). In 2001, Dr. Hamburg became vice president for biological programs at the Nuclear Threat Initiative, a foundation dedicated to reducing the threat to public safety from nuclear, chemical, and biological weapons. Since 2005, she has served as the Initiative's senior scientist. Upon Dr. Hamburg's confirmation as FDA commissioner, HHS Secretary Kathleen Sebelius praised her as "an inspiring public health leader with broad experience in infectious disease, bioterrorism, and health policy."

Salmaan Keshavjee, M.D., Ph.D., M.A., Sc.M., is a physician and anthropologist. He is assistant professor in two departments at Harvard Medical School, as well as associate physician at Brigham and Women's Hospital, Dana Farber Cancer Institute, and Faulkner Hospital. At PIH, he is senior MDR TB specialist. From 2006 to 2008, Dr. Keshavjee was research director and deputy country director for the Lesotho Initiative. His clinical research has focused on the implementation of drug-resistant TB treatment projects run by PIH. Since 2007 he has also led PIH's Russia research initiative, coordinating a multidisciplinary team studying treatment outcomes in drug-resistant TB. This work is informing efforts to treat drug-resistant TB in the region, including Central Asia, and has resulted in several manuscripts. Most recently, a report on the treatment of XDR TB for which Dr. Keshavjee is lead author appeared in the *Lancet*. The results of this research in Russia have guided WHO's revised guidelines for the treatment of drug-resistant TB. Dr. Keshavjee served as an editor of this document, which appeared in 2008. He also represents PIH as chair of WHO's Green

Light Committee (GLC) for MDR TB, WHO's principal global structure for expansion of MDR TB treatment. In this capacity, he advises national programs on the clinical and programmatic management of this disease.

Elena Evgenievna Larionova, Ph.D., is a senior research scientist within the Department of Microbiology, Central TB Research Institute (CTRI), Russian Academy of Medical Sciences (RAMS) in Moscow. In 1986 she received her Ph.D. in biology from the State Pedagogical Institute in Moscow. (Microbiology) Gamaleya Epidemiology and Microbiology Research Institute RAMS, Moscow; 2005, 1996–2011 Senior Researcher, Molecular Genetic Lab Microbiological Department, Central TB Research Institute RAMS. Dr. Larionova's scientific interests include: experimental research in differential diagnostics of a tubercular infection; genotyping of *M.tb.* using restriction fragment length polymorphism (RFLP), spoligotyping, and variable number tandem repeat amplification (VNTR-typing); and drug resistance of mycobacteria testing by both microbiological techniques and by detection of genomic point mutations.

Barbara Laughon, Ph.D., is Senior Scientist for TB Drug Development Partnerships in the Office of the Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health. In this role, she promotes research on TB drugs through collaborations among public, private, and multilateral organizations by interfacing with NIAID research grants, cooperative agreements, and contracts focused on preclinical and clinical anti-infective drug development for emerging infectious diseases and biodefense. She is active in the STOP-TB Partnership serving in working groups on New Drugs and HIV/TB, and is an executive member of the not-for-profit Lilly TB Drug Discovery Initiative (www.tbdrugdiscovery.org/). Dr. Laughon has served the Global Alliance for TB Drug Development as Chair, Scientific Advisory Committee, as a founding stakeholder, and as a contributor to the preclinical development of PA-824. She has over 20 years of leadership experience in drug development for HIV, opportunistic infections, and TB through oversight of NIH extramural programs in drug discovery, IND-enabling studies, and clinical trials. She serves as advisor to PEPFAR, the U.S. Federal TB Taskforce, the U.S. CDC TB Trials Consortium, and the Global Fund. Prior to joining the NIAID, Dr. Laughon was an assistant professor of medicine in infectious diseases at Johns Hopkins University School of Medicine. Her research involved the pathophysiology of Clostridium difficile colitis, anaerobic lung abscess, and clinical research on AIDS. Dr. Laughon received her M.S. and Ph.D. in microbiology from the Anaerobe Laboratory at Virginia Tech with a dissertation on the ultrastructure and biochemistry of anaerobic spirochetes. As a postdoctoral scholar at the

University of Michigan, she characterized the pathogenic role of anaerobes in advanced periodontal disease. She is a fellow of the Infectious Diseases Society of America, a member of the American Society for Microbiology, the IUATLD, and the International AIDS Society. She has published over 50 scientific and review articles.

Renzhong Li has been director of the Drug-Resistant TB Department of the Chinese Center for Disease Control and Prevention, located in Beijing, China, since March 2007. From July 1986 to February 2008, he was associate professor at Shandong Provincial TB Dispensary. He received a bachelor's degree in 1986 and a master's degree in 2004 from Shandong Medical University.

Edward Anthony Nardell, M.D., is a pulmonologist with a special interest in TB. He trained in pulmonary medicine at Massachusetts General Hospital, with additional research training at Boston University School of Medicine. While at Boston City Hospital, he became director of TB control for the City of Boston. In 1981 he became chief of pulmonary medicine and director of TB control for the city of Cambridge, positions he held until 2005. His principal academic appointment is as associate professor of medicine, Harvard Medical School, with secondary parallel appointments in the Department of Social Medicine and Harvard School of Public Health. In the early 1980s, Dr. Nardell became medical director of TB control for the Massachusetts Department of Public Health, a position he held for 18 years. In 2002 he joined PIH as director of TB research. In 2005 he left Cambridge Hospital to assume a full-time research position in the Department of Social Medicine and Health Inequalities, Brigham and Women's Hospital, the hospital arm of PIH. He is also a member of the Pulmonary Division at Brigham and Women's Hospital, where he serves on the pulmonary consult service. Dr. Nardell's research interests include the control of MDR TB in Peru, Russia, and other high-burden countries. His special research interest is airborne TB transmission and control. He currently has a project in South Africa, funded by National Institute of Occupational Safety and Health (NIOSH), studying the transmission of MDR TB using large numbers of guinea pigs to quantify the infectiousness of MDR TB patients and the effectiveness of various control interventions, including ultraviolet germicidal irradiation. Dr. Nardell is past president of the Massachusetts Thoracic Society and the North American Region, International Union Against Tuberculosis and Lung Disease. He was the 2005 recipient of the Chadwick Medal of the Massachusetts Thoracic Society.

Dale Nordenberg, M.D., is a principal with Novasano Health and Science. He is a physician executive who leverages his experience as a pediatri-

cian, medical epidemiologist, and informatician to deliver strategic, operational, and scientific services to domestic and international clients in the health care and health information technology arenas. Recent projects include the development of a public–private partnership to build laboratory capacity for MDR TB across diverse international settings, which he is currently leading; development of governance structures for the National Biosurveillance System for Human Health; development of a multi-institutional collaboration to revise U.S. Food and Drug Administration (FDA) regulatory processes to establish standards for national laboratory data exchange; and the evaluation of emerging diagnostics related to the gut microbiome from both the scientific and clinical perspectives. For the past few years, Dr. Nordenberg has been working as a health care consultant, first with PricewaterhouseCoopers and then with Novasano. From 2002 through 2007, he held various positions at CDC, including associate director and chief information officer and senior advisor for strategic planning. Dr. Nordenberg has led and participated in many disease surveillance, outbreak response, and bioterrorism preparedness and response activities and associated informatics initiatives. He has worked extensively in the arena of pandemic influenza preparedness and response. He was detailed part time to the Office of the National Coordinator for Health Information Technology in 2004–2005 to catalyze a national strategy for children's health information technology. In 2007 and 2009, Dr. Nordenberg was a member of the Science and Technology Subcommittee of the FDA's Science Advisory Board, which was tasked with the evaluation of science and technology at the FDA. Prior to serving with CDC, Dr. Nordenberg was a founding executive of a company that launched VeriSign affiliates in Latin America and Asia and was a member of the faculty of the Emory School of Medicine, where founded and directed the Office of Medical Informatics for the Emory University Children's Center. He has served on the boards of numerous companies. Dr. Nordenberg is a board-certified pediatrician. He received a B.S. in microbiology from the University of Michigan and his medical degree from Northwestern University, and completed his training in pediatrics at McGill University, Montreal Children's Hospital. He completed his fellowship in epidemiology and public health in the Epidemic Intelligence Service program at CDC.

Mikhail I. Perelman, M.D., is chief of phthisiopulmonology and thoracic surgery at I.M. Sechenov's Moscow Medical Academy. Since 1986 he has been academician of the Russian Academy of Medical Sciences (RAMS). He has also held the rank of corresponding member of the USSR Academy of Medical Sciences (1980) and professor of surgery (1964). Academician Perelman received his medical degree in 1945 from Jaroslavl Medical Institute. Prior to joining the Moscow Medical Academy in 1981, Academi-

cian Perelman was chief of thoracic surgery at Moscow's National Center for Surgery. He served as the chief of thoracic surgery at the Institute for Experimental Biology and Medicine in Novosibirsk from 1958 to 1962 and was assistant professor at the Central Institute for Continued Medical Education from 1955 to 1958. His public posts have included president of the Russian Society for Phthisiology, national delegate in the Societe Internationale de Chirurgie, and general secretary of USSR Society of Surgeons. He participates in a number of international professional organizations and honorary membership organizations and is active in international journal editorial staffs (*International Trends in General Thoracic Surgery* and *World Journal of Surgery*).

Carlos M. Pérez-Vélez, M.D., D.T.M.H., is an adult and pediatric infectious disease physician. He is originally from Medellín, Colombia, where he attended medical school and completed a rotating internship, both at the University of Antioquia. He completed a research fellowship in allergy and immunology at Yale University and a residency in internal medicine and pediatrics at New Jersey Medical School, University of Medicine and Dentistry of New Jersey. He also obtained a diploma of tropical medicine and hygiene from the Gorgas Memorial Institute of Tropical and Preventive Medicine of the University of Alabama. After completing fellowships in adult and pediatric infectious diseases at the University of Colorado and the Children's Hospital, he joined the faculty of National Jewish Health and of the University of Colorado School of Medicine. In 2006, he established a TB clinical research field site in the city of Buenaventura in Southwestern Colombia, which he currently maintains with his research team, the Grupo Tuberculosis Valle Colorado. The team is carrying out a diagnostic study comparing alternative specimen collection methods to improve the bacteriological confirmation of pulmonary TB in children, as well as a drug resistance study in this population.

Benjamin Potashnikov is Development Director of Biocom. Mr. Potashnikov's education background includes: North-Caucasus State Technical University (1996–2001), with a specialization in finance and credit and a course of studies in good manufacturing practices (GMP). Mr. Potashnikov also specialized in solid pharmaceutical manufacturing and practical guidelines. Mr. Potashnikov's main interests include regulatory affairs, export, contract manufacturing, marketing, research and development, supplies, external economic activity, and sales.

Gary Reubenson, MBBCh, FCPaeds, DCH, DTM&H, is a pediatrician working at Rahima Moosa Mother and Child Hospital, University of the

Witwatersrand, Department of Pediatrics and Child Health, in Johannesburg, South Africa. In 2004 Dr. Reubenson initiated an outreach service for Sizwe Hospital, the provincial MDR TB treatment facility, primarily to provide assistance in the hospital's management of HIV-infected pediatric patients; this effort also provided an opportunity to learn more about pediatric drug-resistant TB. Since 2005, Dr. Reubenson has been a member of the Gauteng Provincial Expert Panel on the management of MDR and XDR TB in the province.

Svetlana Safonova, Dr.Sci.Biol., is chief bacteriologist of Russia's Federal Correction System. She is a doctor of biology and recognized expert in microbiological diagnostics of TB. Dr. Safonova coordinates all bacteriological laboratories under the Russian implementation system.

Elina Sevastyanova, D.Sc., is a senior research scientist within the Department of Microbiology, Central TB Research Institute (CTRI), Russian Academy of Medical Sciences (RAMS). Her educational background includes Moscow Technological Institute of Food Industry, Department of Microbiology (1981–1986); postgraduate studies at the Microbiology Department of Moscow Technological Institute of Food Industry (1986–1989); candidate of sciences (Ph.D.), specializing in biotechnology (1990); initial specialization in phthisiology and pulmonology at CTRI (1997); WHO-recommended microbiological diagnosis of TB at CTRI (1998); and doctor of sciences (D.Sc.), specializing in microbiology (2010). Throughout her career, Dr. Sevastyanova has completed a number of WHO training courses covering such topics as methods of microbiological diagnosis of TB, management of TB at the district level, and training for the management of laboratory networks in the National Tuberculosis Control Program. Dr. Sevastyanova's main research interests include mycobacteriology, smear microscopy, culture examination, drug susceptibility testing, organization of TB microbiological diagnosis and TB laboratory service, biosafety in TB laboratories, elaboration of methods for improving microbiological diagnosis of TB in the Russian Federation, and preparation of normative documents concerning microbiological diagnosis of TB.

Sonya Shin, M.D., M.P.H., is an associate physician in the Division of Global Health and Division of Infectious Diseases at Brigham and Women's Hospital and assistant professor at the Harvard School of Medicine. She has worked with PIH for 18 years. Dr. Shin's area of expertise is in community-based collaborations to provide complex health interventions in resource-poor settings. She has worked in Peru, Russia, Boston, Haiti, and elsewhere in operational research and programmatic scale-up of such interventions.

Tatiana G. Smirnova, Ph.D., is senior researcher, molecular-genetic research laboratory at the CTRI of RAMS, Moscow. In 2005 she received her Ph.D. in microbiology from Gamaleya Epidemiology and Microbiology Research Institute of RAMS, Moscow. From 1998 to 2006 she was a researcher in the molecular-genetic research laboratory at CTRI. Dr. Smirnova studied at the Russian State Medical University in Moscow from 1992 to 1998. Dr. Smirnova's scientific interests include: genotyping of *M.tb*. using different techniques; quantitative polymerase chain reaction (PCR) real-time; and carrying out of experimental research in TB infection *in vivo* (development of different model of tuberculosis infection in mice), *ex vivo* (infection of eukaryotic cell culture with *M.tb*.), and *in vitro* (investigation of new anti-tuberculosis drug effect against *M.tb*. strains).

Janet Tobias is a media/technology executive and an Emmy award-winning director/producer with 20 years experience working for all three American networks, PBS, Discovery, and MSNBC. Ms. Tobias started her career at *60 Minutes* as Diane Sawyer's associate producer. At *60 Minutes* she distinguished herself working on a wide range of domestic and international stories including: a portrait of the Yakuza, the Japanese organized crime syndicate, and investigations into the lack of regulation in infertility treatment and the abuse of boys in a Guatemalan orphanage. Ms. Tobias moved with Ms. Sawyer to ABC News to launch *Prime Time Live*. At ABC she produced/directed both domestic and international stories ranging from a case study of organ donation to a portrait of the Kuwaiti royal family after the first Gulf War. After a short stint away from the networks to write a feature film screenplay, Ms. Tobias returned to NBC and moved into management at *Dateline NBC*. As a national producer at *Dateline NBC*, she supervised pieces on medical ethics and the home health care industry. She also continued to produce/direct her own stories ranging from a historical look back at Soviet misinformation campaigns to an investigation into oil development in the Ecuadoran rainforest. Ms. Tobias left NBC News to become an Executive Producer at VNI (which became New York Times Television). There she supervised the production of a foreign news show and reporting on a variety of foreign stories including an award-winning piece on rape as a war crime in Rwanda that appeared on *Nightline*. Ms. Tobias then returned to ABC News to head up editorial activities at its newly created Law and Justice Unit where she reported, directed, and supervised legal and criminal justice stories for all ABC news programs: *Nightline*, *20/20*, *World News Tonight*, and *Good Morning America*. In 1998 Ms. Tobias and begin working as an executive with PBS, where she developed and produced programming not only for PBS but also joint projects with ABC and Discovery. She continued her directing and writing career winning two American Bar Association silver gavels for a 4-hour

Frontline/Nightline project on the juvenile justice system in California. In 2001, she launched *Life 360*, a weekly PBS series hosted by Michel Martin that combined documentary pieces with dramatic and comic monologues. *Life 360* launched just after 9/11 to laudatory reviews and won an Emmy in its first season. In 2002, Ms. Tobias ventured into the technology world when she joined Sawyer Media Systems, a Sequoia backed creator of video technology for the web. At Sawyer, Ms. Tobias was Vice President of Production and a member of the executive committee. Clients at Sawyer Media Systems included: Cisco, Genentech, Purina, Nextel, and Autodesk. At the same time, Ms. Tobias continued to be involved in documentary production through her own company Sierra/Tango Productions. At Sierra/Tango she developed and supervised 17 films for MSNBC on a variety of social issues ranging from illegal immigration to the life of teenagers in America. In 2004, she branched further into new media working as a founding partner of Ikana Media. Ikana Media is a digital strategy and production company whose primary focus is on health care information. Clients include AARP, Johnson & Johnson, Cisco Systems, Time Inc., and both WNET and WGBH. At Ikana, Ms. Tobias leads the strategy and creative work. Over the past 5 years she has worked with a variety of clients in the health care space on subjects ranging from broad-based delivery of health care information to communications efforts around obesity and HIV/AIDS. Her focus areas: looking at business opportunities in health care information, technology and health care in the third world, designing digital plans for health care communication, and creating innovative rich media content focused on health, wellness, and medical research. In addition, Ikana Media has produced a variety of television programs covering medical issues. The subjects of two recent films for MSNBC were innovation in neurosurgery and the need for physical and psychological support for soldiers returning from Iraq. In addition to her National Emmy and Bar Association awards, other awards include two Cine Golden Eagles, two Casey medals for meritorious journalism, a National Headliner Award, a Sigma Delta Chi Award, and honorable mention Robert F. Kennedy Journalism and Overseas Press Awards. Janet Tobias is a member of the Writers Guild of America and a graduate of Yale University. She serves on the boards of Healthright International, Mindset Media Society, Rwanda Works and SochiReporter. She served from January to September 2009 as a senior fellow at the University of British Columbia, Sauder School of Business Centre for Sustainability and Social Innovation.

Irina Vasilyeva, D.Sc., is head, associate professor within the Department of Phtisiopulmonology at the CTRI of RAMS in Moscow. Dr. Vasilyeva's education background includes: I.M. Sechenov's Moscow Medical Institute (M.D.) from 1984 to 1990; postgraduate studies in pulmonology and TB at

the CTRI from 1990 to 1994; Candidate of Sciences (Ph.D.) in phtisiopulmonology at the CTRI in 1997; and Doctor of Medical Sciences (D.Sc. Medicine), phtisiopulmonology at the CTRI in 2002. Throughout her career Dr. Vasilyeva has completed a number of international training courses such as: "Tuberculosis Comprehensive: International Approaches with Special Emphasis on MDR Training Program" at the University of Medicine and Dentistry of New Jersey (UMDNJ); "Tuberculosis Training Programme" at the German Central Committee against Tuberculosis in Berlin, Germany; "Regional Training in TB Control Programme Management" through the WHO/KNCV Tuberculosis Foundation; "WHO Training Course for TB Consultants," through the WHO/Center for Control of TB and Lung Diseases in Europe. Dr. Vasilyeva's primary research interests include: clinical research in pulmonary TB; treatment of MDR/XDR TB; clinical trials; molecular-genetic drug susceptibility testing; TB programmatic management; and the writing of treatment guidelines for TB and MDR TB. Dr. Vasilyeva is a WHO expert and author of 105 scientific publications.

Marina Yakimova, Ph.D., is a leading researcher within the Department of Epidemiology, Medical Statistics and Information Technologies, Central TB Research Institute (CTRI), Russian Academy of Medical Sciences (RAMS). Dr. Yakimova's education background includes Tashkent Medical Academy (1971–1977), speciality—therapy, postgraduate studies at the Institute of Medical Genetics of RAMS (1981–1984), Candidate of Sciences, Ph.D. thesis "Genetics of Lung Diseases" (1984). Specialization in phthisiology and pulmonology at Central TB Research Institute of RAMS (2004). Throughout her career, Dr. Yakimova has completed a number of WHO training courses. Dr. Yakimova's main research interests include early diagnosis of TB at general health care institutions, TB epidemiology in the regions of Russian Federation, differential diagnostics of TB and other lung diseases, preparation of normative documents on medical aid to TB patients. Dr. Yakimova is a WHO independent expert

Danila Zimenkov, M.D., Ph.D., received his M.D. in 1999 in biophysics and radiation safety from the Moscow Engineering Physics Institute, Russia. In 2005 he received his Ph.D. in molecular biology from the Institute of Genetics and Selection of Industrial Microorganisms (GosNIIGenetika), From 1998 to 2008, Dr. Zimenkov worked at the closed joint stock company Ajinomoto-Genetika Research Institute in a number of positions of increasing responsibility—from laboratory assistant to group leader. Since April 2008, Dr. Zimenkov has held the position of researcher at the Laboratory of Microbiology Biochips, Engelhardt Institute of Molecular Biology, Moscow, and researcher at Biochip-IMB company.

Paul Zintl, M.P.A., is chief operating officer for Partners In Health (PIH) and senior advisor for planning and finance for the Program in Infectious Disease and Social Change (PIDSC) at Harvard Medical School. He joined PIH and Harvard Medical School in January 2002. Previously, Mr. Zintl was a managing director of J.P. Morgan & Co. in New York, where he worked for 18 years, until 1995. In this capacity, his responsibilities included management, control, analysis, and evaluation of the firm's trading businesses. After leaving J.P. Morgan, he studied state criminal justice systems and worked as a private consultant for 2 years. In 1998 he received a master in public administration degree from the John F. Kennedy School of Government at Harvard.